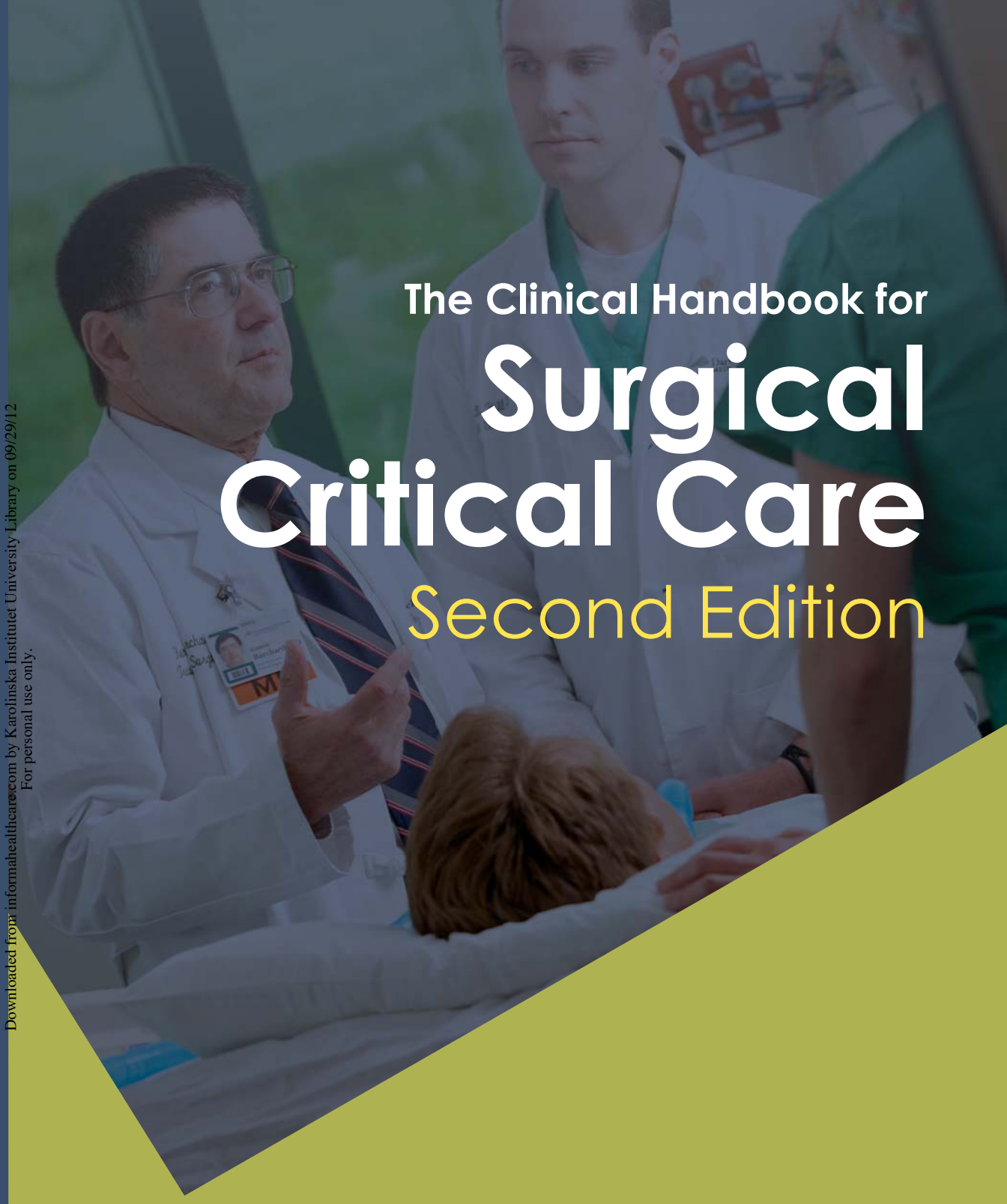

The Clinical Handbook for Surgical Critical Care

Second Edition

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Published in 2012 by Informa Healthcare, 119 Farringdon Road, London EC1R 3DA, UK.
Simultaneously published in the USA by Informa Healthcare, 52 Vanderbilt Avenue, 7th Floor, New York, NY 10017, USA.
Informa Healthcare is a trading division of Informa UK Ltd. Registered Office: Informa House, 30–32 Mortimer Street, London
W1W 7RE, UK. Registered in England and Wales number 1072954.

A CIP record for this book is available from the British Library.
Library of Congress Cataloging-in-Publication Data available on application

ISBN: 978-1-84184-922-5
eISBN: 978-1-84214-588-3

Orders may be sent to: Informa Healthcare, Sheepen Place, Colchester, Essex CO3 3LP, UK
Telephone: +44 (0)20 7017 6682
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Typeset by Exeter Premedia Services Pvt Ltd, Chennai, India
Printed and bound in the UK

Dedication

This book is dedicated to my wife, Marion, my son, Paul, and all who encounter the evaluation and management of the surgical patient with critical illness.

Contents

Online features

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1 | The critical care surgeon

While the designation of a specialized hospital site for immediate postoperative care dates back to the early 1940s, the creation of surgical intensive care units with a capacity for days of monitoring and management did not emerge until about two decades later. Prompted by the poliomyelitis epidemic of the 1940s, the demand for effective mechanical ventilation resulted in positive pressure ventilators, which became more widely utilized in these new intensive care settings.

Over the ensuing decades, the initial primacy of airway and breathing support has been equaled by the implementation of monitoring and manipulation of the circulation. This has been accompanied by improvements such as better use of blood products, renal replacement therapy, transplant surgery, emergency cardiac interventions, novel anesthetic agents, new antibiotics, etc (1).

These advancements have prolonged and saved the lives of patients with surgical critical illness, resulting in not only these better outcomes, but also a monumental effort at clinical and experimental investigation to elucidate the fundamental pathophysiology of these disorders and principles of management.

Since the beginning of critical care concepts, surgeons have been actively engaged in patient care, education, leadership, and scholarly pursuits linked to surgical critical illness. By 1987, the American Board of Surgery recognized that surgeons with a special interest and expertise in surgical critical illness should be acknowledged with subspecialty board certification.

Since the 1980s, subspecialization within the context of general surgery has become more prevalent with and without subspecialty board certification, especially in academic medical centers (2). Vascular surgery, surgical oncology, colorectal surgery, and minimally invasive surgery, for instance, have become common arenas of expertise with little or no regular exposure to patients with surgical critical illness.

In contrast, trauma surgery, another common practice of special interest, has maintained an active surgical critical care component with fellowship trainees expected to attain surgical critical care board certification. This special qualification of the trauma surgeon combined with infrequent exposure of other general surgery specialties to surgical critical illness has been a principle underpinning to the creation of yet another specialty—the acute care surgeon.

THE ACUTE CARE SURGEON

The acute care surgeon combines the interests and expertise of the trauma surgeon, the critical care surgeon, and the general surgeon who attends "time-sensitive" surgical conditions. The expectation that many sociological, training, and practice preference features will demand an increasing workforce of acute care surgeons has resulted in the plan for fellowship training in the specialty of acute care surgery (2–4). Training in surgical critical care is a fundamental component of this new training paradigm, and this manual is designed to assist that training, especially from the perspective that surgical critical illness is, indeed, a surgical condition best understood and manipulated by surgeons.

THE CRITICAL CARE SURGEON TRAINEE

The trainee in surgical critical care characteristically proceeds through three phases in achieving competence in the primary goals of surgical critical care. The first phase is exemplified by the question "Where is the hole?". This refers to the early encounters of a trainee (usually first and second year general surgery residents) with a patient who is typically suddenly ill and the trainee's efforts to define the primary, sometimes life-threatening, organ alteration that needs immediate attention (Table 1.1). For instance, sudden hypotension after major abdominal surgery might prompt questions about hypovolemia, anesthetics, and myocardial infarction.

Table 1.1 The Surgical Trainee in Critical Care Examples of Question Related Problems

1. Where is the hole?
   A. Hypotension
   B. Respiratory distress
   C. Oliguria
   D. Fever
   E. Mental status change
2. How do I plug the hole?
   A. IV fluid
   B. Packed RBCs
   C. Inotropes
   D. Ventilator
   E. Diuretics
   F. Sedatives
3. Why is the hole there?
   A. Bleeding
   B. Infection
   C. Missed intra-abdominal injury
   D. Anastomotic leak
   E. Pulmonary embolism
   F. Myocardial infarction

The trainee's next question is "How do I plug the hole?". Asking this, the trainee (usually a second or third year resident) who has decided that the hypotension is from hypovolemia considers the type and amount of intravenous fluid to administer.

The third question is "Why is the hole there?". This question is best answered when one has knowledge about the surgical disease and surgical procedure. This is the principle focus for the education of more senior trainees, especially a surgical critical care or acute care fellow. This question frequently drives sophisticated surgical decision making. Is there an anastomotic leak? Is there an ischemic left colon? Does this patient need additional surgery?

I proffer that answering the question "Why is the hole there?" is the most important determinant of the outcome for critically ill surgical patients.

THE PRACTICING SURGEON

Even in the setting of an elective surgical practice or a nearby acute care surgery institution, every practicing surgeon can be faced with managing disease in keeping with the primary goals of surgical critical care. Trauma, intestinal hemorrhage, intestinal perforation, leaking anastomoses, and pancreatitis are common examples of disease states that could provide such a challenge and opportunity. The fundamentals of good surgical care—resuscitation of the circulation, debridement of dead tissue, drainage of infection, and minimizing surgical trauma—all diminish the risk of cellular injury, organ malfunction, and the associated morbidity and mortality threats.

It is often difficult, however, for practicing surgeons to maintain current knowledge of advancements in monitoring and technology, which provide more information and sometimes enhanced management of the "How do I plug the hole?" issues of surgical critical care. In addition, the practicing surgeon may not encounter critically ill patients with sufficient frequency to recognize immediately how a problem with the circulation or respiration may relate to the underlying surgical disease or procedure. Thus, the practicing surgeon may have difficulty answering the question "Why is the hole there?" for some patients.

THE CLINICAL HANDBOOK FOR SURGICAL CRITICAL CARE

The purpose of this handbook is to assist the surgical/critical care trainee and the practicing surgeon with all three questions related to surgical critical care and to emphasize the question

"Why is the hole there?". Since much of surgical critical illness is secondary to shock, this topic will begin the guide and will be given special consideration in each subsequent chapter, as appropriate. Shock is the principle "hole" that must be effectively plugged to prevent or diminish cell and organ injury. Discerning the etiology of shock becomes linked to a mature understanding of surgical disease and intervention. Effective surgical critical care decision making then becomes the principle attribute of the sophisticated practitioner of surgical critical care, an expert in discerning "Why is the hole there?".

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2 | Shock

Those who cannot remember the past are condemned to repeat it.
—George Santayana (1863–1952)

HISTORIC CONCEPTS OF SHOCK

From the latter half of the nineteenth century through the twentieth century, the concepts and definitions of shock have been varied and often considered mutually exclusive (Table 2.1). During the first half of the twentieth century, the advocates of hypovolemic hypoperfusion as the principle etiology of shock (e.g., Blalock and Wiggers) vigorously opposed the advocates of circulating toxins as the mechanism (e.g., Cannon) (1–4). As the twenty-first century has proceeded, this same advocacy continues, but the necessity of exclusivity has dissipated.

The concept of shock that will be emphasized in *The Clinical Handbook for Surgical Critical Care* also has a historic underpinning. In 1872, Samuel D. Gross offered the analysis that during shock "… the machinery of life has been rudely unhinged …"—a formulation that allows for a coalescence of etiologies rather than strict separation (5).

Today, shock can be considered a manifestation of total body cell metabolic disturbance—an unhinging of life machinery most vigorously manifested by decreased total body oxygen consumption. The principle etiologies of this alteration are still connected to the twentieth-century debate. Too little oxygen delivery and too much inflammatory toxin both are capable of producing shock. In fact, these two processes are not mutually exclusive, but are characteristically additive threats to cell function. Simply stated, *hypoperfusion begets inflammation, and inflammation begets hypoperfusion* (Table 2.2).

Shock from severe hypoperfusion and severe systemic inflammation is the cause of death and/or multisystem organ failure in surgical critical illness. Understanding these mechanisms of cell metabolic threat can augment all features of surgical critical care evaluation and management (Where is the hole? How do I plug the hole? Why is the hole there?). Therefore, repeating the history of shock concepts from Gross through Cannon, Blalock and Wiggers to more modern contributors like Gann and Rivers can prove more a reward than a condemnation (6,7).

SHOCK AND DECREASED OXYGEN UTILIZATION

Decreased Oxygen Delivery

Oxidative phosphorylation is the primary metabolic process whereby mammalian cells produce cellular energy and heat. Ninety percent of oxygen utilization occurs in the mitochondria and ATP production accounts for 80% of oxygen consumption (8). While deficits in arterial oxygen saturation and blood hemoglobin concentrations can limit oxygen delivery to cells, most often a reduction in blood flow (hypoperfusion) is responsible for diminished oxidative phosphorylation. When total body oxygen delivery is sufficiently compromised, total body oxygen consumption must decrease, a condition termed "delivery-dependent oxygen consumption" Figure 2.1, (9). The inflection point where the increasing consumption curve levels off has been termed as the "critical" oxygen delivery state of that preparation. Oxygen consumption that is delivery dependent and below critical is associated with evidence of cellular energy deficits (e.g., lactic acidosis and hypothermia) (10,11).

In 1942, Cuthbertson described metabolic alterations following tissue injury and linked the combination of hypothermia and decreased oxygen consumption to a reduction in cell vitality, which he termed as the "Ebb Period" or "Ebb Phase." Most of The Ebb Period was secondary to "tissue asphyxia" and associated with a high mortality rate (12,13).

When minute by minute oxygen delivery is insufficient to meet oxidative phosphorylation demands, this is termed an oxygen *deficit*. When the deficit continues over many minutes, then the product of deficit and minutes is termed as the oxygen *debt*. Global hypovolemic hypoperfusion (decreased cardiac output from decreased intravascular volume) is the most

Table 2.1 Common Concepts of Shock – Early 20th Century

1. Disorder of the circulation
2. Disorder of the nervous system
3. Disorder of the endocrine system
4. Toxemia

Table 2.2 Relationship Between Inadequate Oxygen Delivery (Hypoperfusion) and Inflammation – Examples (35–39)

1. Inadequate oxygen supply begets inflammation
   A. Ischemia/reperfusion
   B. Activated PMNs during hemorrhagic shock
   C. Elevated IL-1, IL-6, TNF after hemorrhagic shock
   D. PMN and complement activation after cardiac arrest
   E. Elevated IL-6, CRP during high-altitude exposure
2. Inflammation begets hypoperfusion
   A. Decreased vascular volume
   B. Venous vasodilation
   C. Myocardial depression
   D. Microvascular alterations

Abbreviations: PMN, polymorphonuclear leukocyte; IL-1, interleukin 1; IL-6, interleukin 6; TNF, tumor necrosis factor; CRP, C reactive protein.

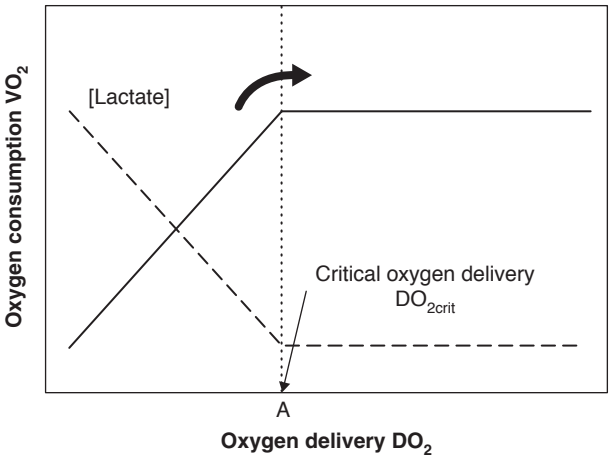

Figure 2.1 A schematic representation of oxygen consumption and oxygen delivery depicting the point when consumption becomes delivery-dependent DO_{2crit}. *Source*: From Ref. 10.

common cause of oxygen debt and the Ebb Period of shock. The magnitude of this debt has been directly correlated with mortality and organ failure risk (14–16).

Cytopathic Hypoxia

After the cell injury associated with the Ebb Period and oxygen debt, normalization or augmentation of the circulation typically results in an increase in oxygen consumption and heat production that Cutherbertson termed as the "Flow Period" (also called the "Flow Phase"); this is a circumstance associated with improved survival as documented over the last several decades (12,17). While oxygen consumption greater than basal does not preclude mortality, the inability to increase oxygen consumption following improved oxygen delivery is highly lethal and akin to failure to emerge from the Ebb Period (17–20). This alteration in cell metabolism has been termed "cytopathic hypoxia," whereby mitochondrial oxidative phosphorylation is

impaired by mechanisms such as inhibition of pyruvate dehydrogenase, nitric oxide inhibition of cytochrome A and A_3, as well as alterations in the enzyme poly(ADP-ribose) polymerase (21). The most common clinical association with this deficit in cell oxygen utilization is severe systemic inflammation (18,21).

SHOCK AND INCREASED OXYGEN UTILIZATION

While decreased cellular oxygen consumption is the premier indication that the machinery of life is unhinged, resuscitation of the circulation, augmented oxygen delivery, and increased oxygen consumption do not preclude the onset of organ failure and mortality (22). Under these circumstances, severe systemic inflammation is, again, the most common illness, and several concepts have been offered to explain these morbidity and mortality threats.

Attempts to link organ failure to direct cell injury via mechanisms such as apoptosis, autophagy, pyroptosis, necrosis, and oncosis have not been supported by autopsy findings in patients with multisystem organ failure, although such findings have not been juxtaposed to oxygen delivery and consumption measurements (23–25). Instead, clinical and pathological data infer that vital organ cell function can suffer a metabolic deficit that is not perfectly associated with decreased oxygen utilization, and that this insult is less lethal. Presumably, the patients who died and were autopsied, had a more severe alteration than the patients who had lived, even then the evidence for marked cellular anatomical damage is meager.

Therefore, a more subtle mechanism of rude unhinging is becoming evident, indicative of a cellular metabolic deficit that does not necessitate decreased oxygen utilization. Studies, such as that of Eastridge, which demonstrate cell membrane malfunction with systemic inflammation and little evidence of severe hypoperfusion, are in keeping with this concept (7). Several authors have offered hibernation as a mechanism of decreased cell energetics and cell protection during shock, but hibernation is associated with decreased oxygen consumption, the marker for the highest mortality risk (22,24). It is possible that an increase in oxygen consumption is not meeting upregulated cell energy demand, but attempts to augment supranormal oxygen consumption further have not regularly met with success (26). In summary, the terminology "pathologic metabolic downregulation" as offered by Levy is a more modern-day language equivalent of rude unhinging, is but indicative of the same fundamental concept of altered cell energetics during the various phases of shock.

MULTIPLE ORGAN DYSFUNCTION AND THE MULTIPLE "HIT" HYPOTHESIS

The multiple organ dysfunction syndrome (MODS), also designated as multiple organ failure (MOF), is recognized as the most common cause of death in surgical intensive care units in the developed world (27). While the first description of sequential organ failure was linked to the severe hypoperfusion that accompanies a ruptured abdominal aneurysm, later descriptions have emphasized the linkage to severe systemic inflammation (27–30). Typically, patients who develop MODS have been resuscitated through the Ebb Phase and exhibit continuing or progressive organ malfunction into the Flow Phase.

Patients in the Flow Phase are subject to additional threats ("hits") that have been broadly catalogued into two mechanisms: aggravated hypoperfusion and aggravated inflammation. While such additional hits may be grossly evident (e.g., massive upper gastrointestinal hemorrhage, *Escherichia coli* bacteremia), more often the evidence for aggravated hypoperfusion and inflammation is more subtle (e.g., deficits in microcirculation, progressive increase in proinflammatory cytokines) (31–33). As described above, these mechanisms of continuing cellular insult are not mutually exclusive and, in fact, are, for all intents and purposes, inseparable (*hypoperfusion begets inflammation, inflammation begets hypoperfusion*). Therefore, as outlined below and more fully described in the chapters on the circulation and inflammation, prompt and then continuing attention to oxygen delivery and systemic inflammation are the principles that limit the rude unhinging of cellular metabolism, organ failure, and mortality in surgical critical illness.

THE CLINICAL DIAGNOSIS OF SHOCK

> … shock is a general bodily state … and is characterized by a persistent reduced arterial pressure, by a rapid thready pulse, by a pallid or grayish or slightly cyanotic appearance of the skin which is cold and moist with sweat, by thirst, by superficial rapid respiration, and commonly by vomiting and restlessness, by a lessened sensibility and often by a somewhat dulled mental state.
>
> —Walter Cannon, Traumatic Shock, 1923

The Ebb Phase

During World War I, Walter Cannon, a Harvard physiologist who had been studying the circulation, traveled to France to study war wounds and was provided with a large experience with humans exhibiting the alterations described above. Sometimes, these signs and symptoms developed quickly after injury (which Cannon called *primary* shock), while sometimes these were delayed by several hours (called *secondary* shock). Primary shock was considered a consequence of massive hemorrhage, and secondary shock a consequence of tissue injury (3). Regardless of the timing, these wounded soldiers were exhibiting the clinical features characteristic of severe hypovolemic hypoperfusion, oxygen delivery less than $O2D_{crit}$, and shock in the Ebb Phase (Table 2.3).

One would expect that most providers would be quick to recognize the most severe manifestations of shock in the Ebb Phase, even when a cardiogenic or an inflammatory etiology is responsible. However, some patients, such as those described by Gross, do not exhibit such obvious clinical alterations and require a more careful examination to discover the "… deep mischief lurking in the system" (5). Usually, this more careful examination is achieved through simple laboratory and/or radiographic studies (Table 2.3). These parameters either identify a

Table 2.3 Clinical Features of Shock in the Ebb Phase (40–49)

I. Physical examination
  A. Circulation
    i. Hypotension (not subject to an absolute number)
    ii. Tachycardia (not subject to an absolute number)
    iii. Cool, pale, possibly cyanotic extremities
    iv. Delayed capillary refill
  B. Respiration
    i. Tachypnea
    ii. Preserved arterial oxygenation - hemorrhage
    iii. Disturbed arterial oxygenation - inflammation
  C. Mental status
    i. Delirium
    ii. Coma in most severe cases
  D. Temperature – Hypothermia
    i. Mild - >35 < 37
    ii. Severe - <35°C without external cooling
II. Laboratory evaluation
  A. Metabolic acidosis
    i. Elevated lactic acid
    ii. Diminished base excess
  B. Hypokalemia – principally for trauma
  C. Hyperglycemia – non-diabetic
  D. Low ionized calcium
  E. Radiology
    i. Collapsed IVC on FAST exam
    ii. Collapsed IVC on abdominal CT
    iii. Echocardiogram demonstrating marked wall motion abnormalities

Abbreviations: IVC, inferior vena cava; FAST, focused abdominal ultrasound for trauma; CT, computed tomography.

threat to the circulation (an underfilled inferior vena cava, severe left ventricular compromise) or a threat to cell metabolism, thus improving diagnostic sensitivity.

The Flow Phase

The characteristics of the Flow Phase that are associated with improved survival are a hyperdynamic circulation, increased oxygen delivery and consumption, and an increase in body temperature. The clinical features of this condition are listed in Table 2.4. The Flow Phase may be associated with no evidence of organ malfunction, but more commonly a circulatory disturbance (hypotension from a low systemic resistance) or other organ malfunction is present along with metabolic indicators of a rude unhinging, though typically not as severe as the Ebb Phase. Just as the Ebb Phase can transition into the Flow Phase, additional "hits" can push the Flow Phase back to the Ebb Phase with the attendant mortality risk.

SHOCK MANAGEMENT PRINCIPLES

After the diagnosis of shock is recognized, two therapeutic strategies should be applied—restore/augment oxygen delivery and limit inflammatory toxin production or effect. Simultaneous application of these principles during both the Ebb and Flow Phases is paramount, but, as expected, restoration/augmentation of oxygen delivery is more pressing in the Ebb Phase and efforts to limit inflammation more pressing in the Flow Phase.

Restoration/augmentation of oxygen delivery is usually based on improving cardiac output using the diagnostic and therapeutic methods described in the circulation chapter. Importantly, experimental and clinical data demonstrate that improving oxygen delivery effectively decreases blood inflammatory toxin concentrations, thereby addressing both principles simultaneously (6,34).

Limiting inflammatory toxin effect is assisted by the diagnostic and therapeutic processes described in the inflammation chapter. Since inflammation can disturb both the macro- and microcirculation, treatment of inflammatory toxin production and/or effect can result in improved oxygen delivery, most evident when myocardial depression accompanies sepsis and resolves as the infection subsides (35).

Table 2.4 Clinical Features of Shock in the Flow Phase (50)

I. Physical examination
A. Circulation
i. Hypotension (not subject to an absolute number)
ii. Tachycardia (not subject to an absolute number)
iii. Warm and pink extremities
iv. Brisk capillary refill
B. Respiration
i. Tachypnea
ii. Poor oxygenation
C. Mental status
i. Delirium possible
D. Temperature
i. Hyperthermic
II. Laboratory evaluation
A. Metabolic acidosis
i. Elevated lactic acid
ii. Diminished base excess
B. Hyperglycemia
C. Low ionized calcium
D. Radiology
i. Bilateral pulmonary infiltrates
ii. Shock bowel on abdominal CT
iii. Echocardiogram with hyperdynamic ventricular function

SUMMARY

Surgical critical illness is a consequence of shock and shock is a manifestation of total body cellular metabolic derangement, a rude unhinging of the machinery of life. Insufficient oxygen delivery and exuberant inflammatory toxin effect are the principle etiologies of this metabolic alteration. Astute recognition of shock by clinical examination and common laboratory investigations should then prompt equally astute measures to restore total body oxygen delivery and limit systemic inflammation, thus allowing patients to pass from the Ebb Phase, to the Flow Phase, and to the Survival Phase.

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3 | The circulation

OXYGEN DELIVERY

Oxygen delivery to cells is vital for cell metabolic activity and constitutes the principle function of the cardiopulmonary organ system. Before discussing the cardiovascular component of oxygen delivery, a description of oxygen concentrations at the arteriolar, capillary, and cellular level as well as oxygen affinity for hemoglobin will be presented.

Blood Flow and Diffusion

Oxygen enters the arterioles at pO_2 and hemoglobin saturation close to arterial levels, and the concentration thereafter usually diminishes as the distance along the arteriolar system and capillaries lengthens. The drop in pO_2 and saturation is dependent upon the rate of oxygen extraction by the cells supplied by the arterioles and capillaries, but hemoglobin normally delivers oxygen to transcapillary tissues at a partial pressure of 5–30 mm Hg (1–3).

The diffusion of oxygen from the arterioles and capillaries to the cells is indirectly proportional to the distance of cells from capillaries. Therefore, an increase in the interstitial space may diminish oxygen concentration at the cellular level. Normal mitochondrial pO_2 falls in the range of 4–20 mm Hg. However, mitochondria can function with a pO_2 in excess of only 1 mm Hg (1). Thus, mitochondrial hypoxia is more likely a function of less oxygen reaching the arterioles and capillaries (diminished perfusion, decreased oxygen delivery to the capillaries) rather than diminished diffusion from the capillary to the cell (4).

At the capillary level, oxygen release from hemoglobin is an important aspect of oxygen transfer to the interstitium and, subsequently, to cells. The relationship between hemoglobin saturation and oxygen tension is described by the oxyhemoglobin saturation curve (Fig. 3.1). The position of the oxyhemoglobin dissociation curve along the horizontal axis is described by the P50 value, the oxygen tension necessary to saturate 50% of the hemoglobin (normal, 26.3 mm Hg; adults at sea level) (5). The shape of the curve illustrates that less oxygen is released when pO_2 drops at the higher level (60–100 mm Hg), but more oxygen is released at levels that develop in the capillary circulation (30–50 mm Hg). A shift of the oxyhemoglobin curve to the right (an increase in P50) results in more oxygen release (less oxygen affinity), whereas a shift to the left results in less oxygen release.

Several factors that cause right and left shifts are listed in Table 3.1 (5). 2, 3-Diphosphoglycerate (DPG), a product of erythrocyte glycolysis, is a major determinant and indirectly proportional to hemoglobin–oxygen affinity. DPG is diminished in stored red blood cells and the transfused blood takes more than 24 hours to regain its normal level. Low serum inorganic phosphate levels also result in DPG depletion. Importantly, hypothermia and metabolic alkalosis, commonly seen in critically ill surgical patients, increase hemoglobin oxygen affinity. Therefore, the use of fresh red cells, providing inorganic phosphate intravenously, reversing hypothermia, and correcting metabolic alkalosis, may improve oxygen delivery to the cells.

CARDIOVASCULAR SYSTEM

The major function of the cardiovascular system is to deliver oxygen to the tissues and remove byproducts of metabolism to their sites of elimination (lungs, kidneys, liver). The determinants of total body oxygen delivery are listed with other commonly measured or calculated hemodynamic variables in Table 3.2 (6). As can be seen from this formula, the pulmonary component is limited to providing adequate arterial oxygen saturation (≥90% at a PaO_2 of >60 mm Hg). This is usually readily achieved with modern respiratory therapy. Hemoglobin frequently increases with transfusion, but during a critical illness, concerns about the adverse effects of blood transfusion have been associated with the commonplace acceptance of hemoglobin concentrations in the range of 7–8 gm/dL. Such a reduction in oxygen content (nearly 50% of normal for some patients) is usually well tolerated, indicating that for most surgical critical illness, the delivery

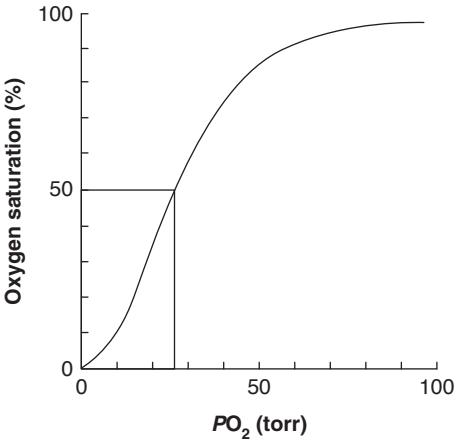

Figure 3.1 Characteristic oxyhemoglobin saturation curve.

Table 3.1 Factors Altering Hemoglobin–Oxygen Affinity

Decreased Affinity	Increased Affinity
• Decreased pH	• Increased pH
• Increased temperature	• Decreased temperature
• Increased pCO_2	• Decreased pCO_2
• Increased DPG	• Decreased DPG
	• Carboxyhemoglobin

Source: Adapted from Ref. 1.

of oxygen to tissues is principally linked to blood flow, that is, cardiac output, rather than blood oxygen content (6–9).

The determinants of cardiac output can be organized both by the variables that affect ventricular function and those that affect venous return. Depending on clinical circumstances, the logical application of one such physiology (physio-logic) may be more suitable than the other, as described below.

Ventricular Physiology

The major determinants of ventricular performance are listed in Table 3.3. Preload represents the magnitude of myocardial muscle stretch before contraction, the stimulus described by the Frank-Starling mechanism (Fig. 3.2), whereby increased stretch leads to increased contraction until the muscle is overstretched. Preload is most appropriately measured as end-diastolic volume (EDV) (10,11). Since volume is not easily measured clinically, the direct proportion between ventricular volume and ventricular end-diastolic pressure (EDP) allows pressure measurement to estimate volume. As described in the section on "Confounding Variables," the pressure–volume relationship (compliance) may change and make pressure measurements difficult to interpret.

Ventricular afterload is determined primarily by the resistance to ventricular ejection present in either the pulmonary [pulmonary vascular resistance (PVR)] or systemic arterial tree [systemic vascular resistance (SVR)]. With constant preload, the increased afterload diminishes ventricular ejection, and decreased afterload augments ejection (Fig. 3.3).

Contractility represents the force of contraction under conditions of a predetermined preload and/or afterload. Factors that can increase and decrease contractility are listed in Table 3.4. A change in contractility, like a change in afterload, will result in a different cardiac function curve (Fig. 3.4).

Table 3.2 Hemodynamic and Oxygen Delivery Variables (2)

Item	Definition	Normal
Central venous pressure (CVP)	CVP = RAP; in the absence of tricuspid valve disease, CVP = RVEDP	5–15 mm Hg
Left atrial pressure (LAP)	Left atrial pressure; in the absence of mitral valve disease, LAP = LVEDP	5–15 mm Hg
Pulmonary artery occlusion pressure (PAOP)	PAOP = LAP, except sometimes with high PEEP levels	5–15 mm Hg
Mean arterial pressure (MAP)	MAP = DP + 1/3 (SP – DP)	80–90 mm Hg
CI Cardiac index	CI = CO/m^2 BSA	2.5–3.5 L/min/m^2 BSA
SI Stroke index	SI = SV/m^2 BSA	35–40 mL/beat/m^2
SVR Systemic vascular resistance	SVR = (MAP – CVP) × 80/CO	1000–1500 dyne-sec/cm^5
PVR Pulmonary vascular resistance	PVR = (MAP – PAOP) × 80/CO	100–400 dyne-sec/cm^5
CaO_2 Arterial oxygen content (vol%)	$CaO_2 = 1.39 \times Hgb \times SaO_2 + (PaO_2 \times 0.0031)$	20 vol%
$C\bar{V}O_2$ Mixed venous oxygen content (vol%)	$C\bar{V}O_2 = 1.39 \times Hgb \times S\bar{V}O_2 + (P\bar{V}O_2 \times 0.0031)$	15 vol%
$C(a - v)O_2$ Arterial venous O_2 content difference	$C(a - v)O_2 = CaO_2\ C\bar{V}O_2$ (vol%)	3.5–4.5 vol%
Oxygen delivery (O_2D or DO_2)	$O_2D = CO \times CaO_2 \times 10$; 10 = factor to convert mL O_2/100 mL blood to mL O_2/L blood	900–1200 mL/min
Oxygen consumption (O_2C or VO_2)	$O_2C = (CaO_2 - C\bar{V}O_2) \times CO \times 10$	250 mL/min 130–160 mL/min/m^2

Abbreviations: BSA, body surface area (m^2); CO, cardiac output; DP, diastolic pressure; LVEDP, left ventricular end-diastolic pressure; PaO_2, partial pressure of oxygen, arterial; PAOP, pulmonary artery occlusion pressure; PEEP, positive end-expiratory pressure; $P\bar{V}O_2$, partial pressure of oxygen, mixed venous; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; SaO_2, arterial oxygen saturation; $S\bar{V}O_2$, mixed venous oxygen saturation; SP, systolic pressure; SV, stroke volume.

Table 3.3 Determinants of Ventricular Function

- Preload
- Afterload
- Contractility
- Heart rate

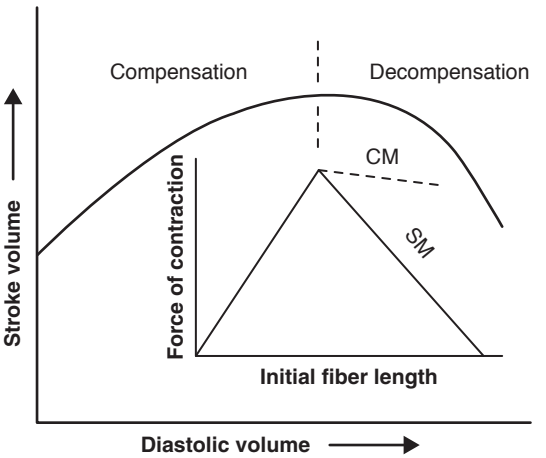

Figure 3.2 Schematic diagram of Starling's law of the heart. The inset demonstrates the difference between cardiac and skeletal muscle, where cardiac muscle does not decompensate as rapidly with increasing stretch.

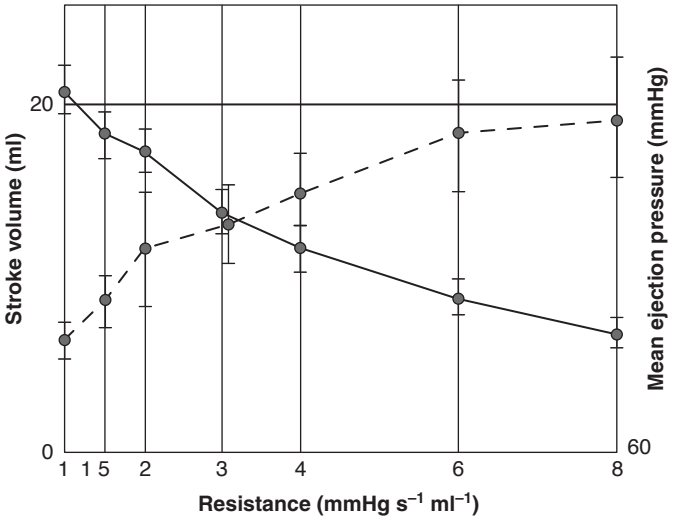

Figure 3.3 The decrease in stroke volume (black line), which develops secondary to an increase in resistance (dotted line).

Table 3.4 Factors Affecting Myocardial Contractility

Increased	Decreased
Catecholamines	Catecholamine depletion/receptor malfunction
Inotropic drugs	Alpha and beta blockers
	Calcium channel blockers
Increased preload	Decreased preload
	Overstretching of myocardium
Decreased afterload	Increased afterload
	Severe systemic inflammation

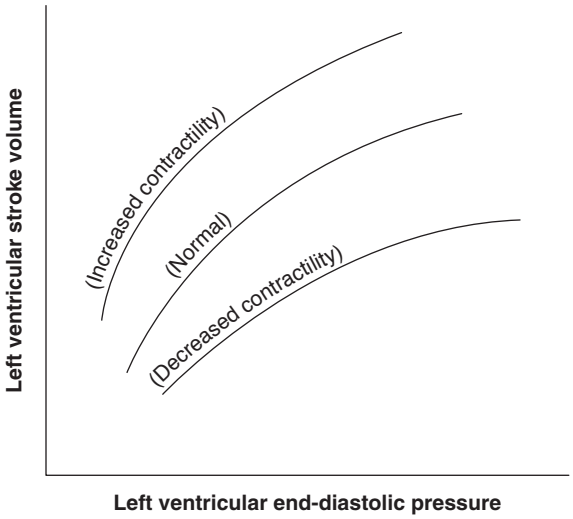

Figure 3.4 Schematic representation of the cardiac function curve with different contractility states.

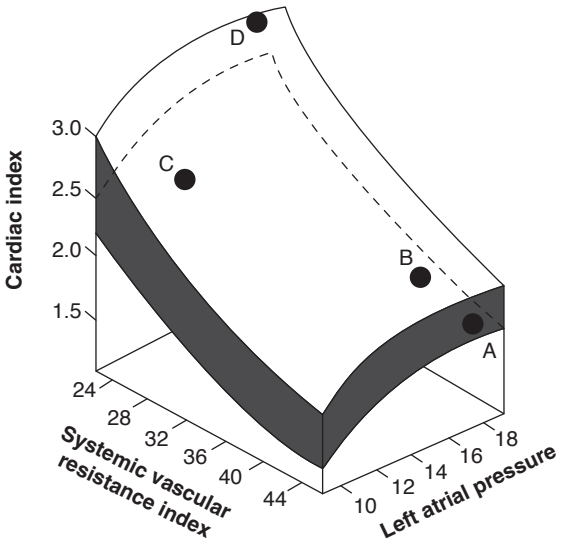

Figure 3.5 Schematic representation of the effects of inotrope (dopamine) administration and afterload reduction (nitroprusside) on cardiac index. Note that afterload reduction also reduced preload and augmentation of preload further increased cardiac index. A, control; B, dopamine; C, dopamine and nitroprusside; D, dopamine and nitroprusside and preload restoration.

The combined influence of increasing contractility and decreasing afterload to improve ventricular function is illustrated in Figure 3.5.

Heart rate is directly proportional to cardiac output (not cardiac muscle mechanics per se) until rapid rates diminish ventricular filling during diastole.

Right and Left Ventricular Differences

The differences in the structure and position of the right and left ventricles can influence the relative importance of each of the determinants of ventricular function listed above. The right ventricle's initial response to increased afterload is an increase in contractility, called homeometric autoregulation. As afterload increases further, the RV can respond to endogenous catecholamines. Subsequently, the RV begins to dilate and augment function via the Frank–Starling mechanism. If this continues, the right ventricle eventually fails (output decreases as preload increases) and the left ventricle may consequently suffer from two mechanisms: diminished preload from poor right ventricular output, and diminished volume from leftward shift of the interventricular septum. Such a failure can be catastrophic (12,13).

Vascular Resistance

The relationship between cardiac output and circulatory pressure is described by the formulae for systemic and pulmonary vascular resistance shown in Table 3.2. Resistance to flow in the systemic and pulmonary artery systems resides mostly in the arteriolar region. This is distinctly different from the venous system where resistance is primarily located in the large veins of the thorax and abdomen.

Arterial vascular resistance is the most common afterload against which the right and left ventricles must eject. Calculation and manipulation of vascular resistance are practical tools for hemodynamic assessment and management of critically ill surgical patients. Table 3.5 lists the common conditions that alter systemic and pulmonary vascular resistance. Note that disease may have variable effects upon the systemic circulation, but almost always increases pulmonary vascular resistance.

Table 3.5 Factors Affecting Vascular Resistance

Systemic	
Increased	**Decreased**
Hypovolemia	Inflammation
CHF	Spinal cord injury
Cardiogenic shock	
Very severe inflammation	Anaphylaxis
Hypocapnia	Hypercapnia
Vasoconstrictors	Vasodilators
Pulmonary	
Increased	**Decreased**
Hypoxia	Vasodilators
Hypercapnia	
COPD	
Bronchospasm	
Pulmonary edema	
Inflammation	
Pulmonary embolism	
Pulmonary contusion	
Pneumonia	
Pneumothorax	
PEEP	

Venous Return

While the term venous return is used commonly, the determinants of venous return are rarely considered in clinical practice. As will be emphasized, in surgical patients, the physiol-logic of augmenting venous return can be more practical as a method of improving the circulation than the logic applied to ventricular function.

Venous return is linked to another important function of the venous system, that is, blood volume capacitance. About 70% of the blood volume is contained in the veins, with the splanchnic and cutaneous veins the largest reservoir regions. The splanchnic reservoir is the principle resource for acute mobilization of blood volume.

Total venous capacitance is the sum of the *capacity* of individual veins. Capacity is the volume contained in a vein at a specific distending pressure. Venous *compliance* is the change in volume (ΔV) of a vein secondary to a change in distending pressure (ΔP). Distending pressure (DP) is not the pressure within the lumen of the vein, but the difference between intraluminal and extraluminal pressure, such that DP is greater than zero if the pressure inside the lumen is greater than the pressure outside (14,15).

When DP is zero, the volume in a vein is designated as *unstressed* (Vu). When DP is greater than zero, the volume in a vein is called *stressed* (Vs). Under resting conditions, about 70% of the venous blood volume is in unstressed veins that serve the reservoir function, but the venous pressure that determines venous return is governed by Vs. The relationship between Vs and Vu and venous return is illustrated in Figure 3.6 (14).

Venous return (VR) is also described by the following formula: (15)

$$VR = \frac{MCFP - CVP}{RV + RA/19}$$

Where, MCFP = mean circulatory filling pressure, CVP = central venous pressure [right atrial pressure (RAP)], RV = venous resistance, and RA = arterial resistance.

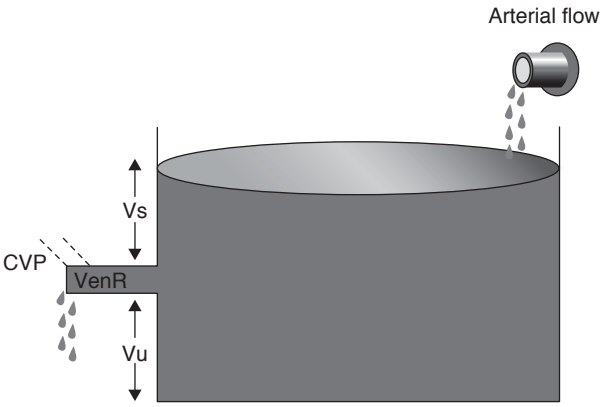

Figure 3.6 Venous return stressed and unstressed volumes—the tub analogy. The water in the tub represents total venous volume and a hole in the tub divides the total volume into stressed (Vs) and unstressed (Vu) volumes. The water leaves the tub depending upon the diameter of the hole (representing venous resistance) and the height of the water above the hole (Vs). An increase in Vs results in an increase in flow. Vu does not affect flow. Moving the hole down (a relative increase in Vs compared with Vu) increases flow. This represents the effect of venoconstriction. CVP is the pressure at the end of the opening that inhibits flow through the tube. *Source*: From Ref. 14.

MCFP is the pressure in small veins and venules, which must be higher in the periphery than CVP so that blood can flow from the periphery to the thorax. RV is located primarily in the large veins in the abdomen and chest. RA is located mostly in the arterioles.

The principal factor determining MCFP is Vs, a variable directly influenced by blood volume (14,15). Additional factors that alter venous return variables are listed in Table 3.6. This list shows that surgical patients frequently have diseases or therapeutic interventions that may inhibit venous return.

Physical Exam of the Circulation

For the surgeon, examination of the cardiovascular system (observing or measuring the parameters listed in Table 3.7) is used primarily to assess total body and regional perfusion. When perfusion is inadequate, then physical exam can provide an assessment of the likely etiology.

Total Body Perfusion

Measurement of the vital signs (systolic and diastolic blood pressure, pulse, respiration, temperature) is the first step of the physical examination. As evident in the calculations in Table 3.2, blood pressure is determined by both cardiac output (flow) and resistance. Frequently, a decrease in blood pressure indicates a decrease in cardiac output (hypoperfusion), especially when the neuroendocrine response to decreased flow causes increased vascular resistance. However, blood pressure may be in the normal range or elevated in the face of hypoperfusion, with conditions such as congestive heart failure (CHF), hypothermia, and in patients with underlying hypertension with a baseline pressure above the normal range. In addition, hypotension may be present during normal or augmented perfusion, such as that occuring in severe inflammation or spinal cord injury, when the reason for a lower pressure is a lower resistance rather than lower flow. Orthostatic hypotension (>20 mm Hg drop in systolic, >10 mm Hg drop in diastolic pressure) is more specific for intravascular volume depletion, but often difficult to obtain in surgical critical care settings.

Tachycardia is a more sensitive indicator of hypoperfusion and orthostatic stress but is less specific and can be a result of various other causes (i.e., anxiety, pain, temperature elevation, delirium). Respiratory rate and depth can be increased as a response to the acidosis of decreased oxygen delivery, but is also subject to other stimuli. Core temperature can be increased in hyperdynamic circulatory states and decreased with severe hypoperfusion (see below).

Table 3.6 Factors Altering Venous Return Variables

I. Increased venous return
  A. Increased MCFP
    1. Increased vascular volume
    2. Decreased venous capacitance
    3. External compression
    4. Trendelenburg position
(increased MSP in lower extremities and abdomen)
  B. Decreased CVP
    1. Hypovolemia
    2. Negative pressure respiration
  C. Decreased venous resistance
    1. Decreased venous compression
    2. Negative pressure respiration
II. Diminished venous return
  A. Decreased MCFP
    1. Hypovolemia
    2. Vasodilation
  B. Increased CVP
    1. Intracardiac
      a. CHF
      b. Cardiogenic shock
      c. Tricuspid regurgitation
      d. Right heart failure
    2. Extracardiac
      a. Positive pressure respiration
      b. PEEP
      c. Tension pneumothorax
      d. Cardiac tamponade
      e. Increased abdominal pressure
  C. Increased venous resistance
    1. Increased thoracic pressure
      a. Positive pressure respiration
      b. PEEP
      c. Increased abdominal pressure
      d. Tension pneumothorax
    2. Increased abdominal pressure
      a. Ascites
      b. Bowel distention
      c. Tension pneumoperitoneum
      d. Intra-abdominal hemorrhage
      e. Retroperitoneal hemorrhage
      f. Edema from an abdominal inflammatory illness
      g. Edema from severe systemic inflammation

With mild-to-moderate hypoperfusion, patients often become restless and agitated, pulling at restraints, intravenous lines, and nasogastric tubes. Severe hypoperfusion can result in obtundation and coma.

Most commonly, hypoperfusion stimulates a neuroendocrine response that results in peripheral vasoconstriction and, consequently, pale to cyanotic and cool to cold extremities. Skin covering the patella is particularly sensitive to hypoperfusion and vasoconstriction here, resulting in "purple knee caps" that may be an early clinical sign of hypoperfusion. Skin temperature (cool vs. warm) may be particularly useful for identifying patients with a hyperdynamic circulation (warm extremities) (16).

Distended neck veins are consistent with impairment of cardiac function, but not always with CHF or cardiogenic shock (17). CVP elevation and neck vein distention may be secondary

Table 3.7 Cardiovascular Physical Exam

Assessment of total body perfusion
1. Blood pressure
2. Pulse
3. Respiration
4. Core temperature
5. Mentation
6. Skin color and temperature
7. Neck veins
8. Heart examination
9. Urine output
Assessment of regional (extremity) perfusion
1. Pulse
2. Color
3. Temperature
4. Pain
5. Movement

to a force exerted outside the lumen of the right atrium (tension pneumothorax, pericardial tamponade, positive end-expiratory pressure (PEEP), prolonged expiration in chronic obstructive pulmonary disease (COPD)].

Examination of the heart focuses on the quality of heart sounds (diminished sounds may represent pericardial fluid or shift of the mediastinum) and the presence or absence of murmurs and/or a gallop. Distinguishing an S3 gallop from an S4 may be difficult, especially with tachycardia. The distinction is important, however, since an S4 is common in patients aged 50 years and above and an S3 is quite specific but not very sensitive for a failing left ventricle (17,18).

Urine output at least 0.5 $cm^3/kg/hr$ is usually considered an indication of adequate total body perfusion. Unfortunately, as described in the section on "Confounding Variables," even this clinical tool must be evaluated with caution. Importantly, examination of the lungs and extremities for evidence of edema is not specific for cardiac dysfunction. As will be emphasized later, in surgical critical illness total body salt and water excess is commonly associated with, at best, a normal, but still too frequently, a decreased intravascular volume. Under these circumstances, relying on the lung or the periphery to draw conclusions about cardiac filling and function can be dangerously misleading.

Regional Perfusion

Physical examination evidence of regional hypoperfusion is limited primarily to the extremities. A painful, pale, pulseless, paralyzed, and cold extremity with paresthesia is diagnostic of acute arterial insufficiency. Chronic arterial insufficiency demonstrates loss of pulse, hair loss, dependent rubor, and sometimes loss of muscle mass. Acute venous obstruction, particularly in the iliofemoral region, may also cause decreased extremity perfusion. The lower extremity may be edematous and white (phlegmasia alba dolens) with little arterial compromise, or edematous and blue (phlegmasia cerulea dolens) with increased muscular pressure sufficient to diminish arterial circulation and cause tissue necrosis, often resulting in skin with fluid-filled bullae.

Physical examination alone is rarely sufficient to evaluate precisely other types of regional hypoperfusion (cerebral, gastrointestinal), but can contribute greatly to the overall clinical evaluation. For instance, evidence of sudden neurologic deficit consistent with middle cerebral artery occlusion or an unremarkable abdominal exam coexistent with severe abdominal pain may lead to the diagnosis of cerebral and intestinal infarction, respectively.

Hemodynamic Monitoring

The purpose of hemodynamic monitoring is to measure the cardiovascular variables that help assess the adequacy of the circulation (where is the hole?), the etiology of an inadequate

circulation (why is the hole there?), and the effect of therapeutic interventions (how do I plug the hole?). In this section, the emphasis will be on the fundamentals of commonly used and emerging hemodynamic monitors, the confounding variables that make a monitor difficult to interpret, methods of reducing confusion, complications of monitoring equipment, and selection of patients for more complex hemodynamic analysis. Except as related to confounding variables and/or complications, no technical details of monitor placement or use will be presented.

Continuous Electrocardiogram Monitoring

Continuous electrocardiogram (EKG) monitoring to record heart rate and indicate arrhythmias is the simplest and most frequently used hemodynamic monitor after standard blood pressure and pulse determinations. While arrhythmias are common in surgical critical illness, a comprehensive review of the diagnosis and management of rhythm disturbance is beyond the scope of this manual.

Measurement of Arterial Pressure

Arterial catheterization is often used to supplement blood pressure cuff measurements with constant monitoring and ease of blood sampling. Under normal conditions, the aortic pressure pulse is altered as the aortic root pressure is transmitted to the peripheral arteries, producing a small increase in systolic pressure and decrease in diastolic pressure (19). Most often the radial and femoral arteries are accessed, while more rarely the dorsalis pedis or brachial arteries. Severe vasoconstriction may impede perfusion of the radial or dorsalis pedis arteries and result in a lower pressure than the aortic root. This may be less so with femoral cannulation, but severe vasoconstriction impeding peripheral pulses is a matter of concern even if a higher pressure is recorded in a larger vessel (20).

Patients with a left ventricular volume that is placed within the upward slop range of the Frank–Starling effect are considered "volume responsive," indicating that ventricular output will increase with greater ventricular muscle stretch and decrease with lesser ventricular muscle stretch (Fig. 3.2). Through effects on CVP and RV, positive pressure ventilation can result in a decrease in venous return and, therefore, lower cardiac output for ventricles that are volume responsive. Thus, beat-by-beat ventricular output, that is, stroke volume, can also be decreased by positive pressure ventilation in volume responsive hearts, causing a decrease in pulse pressure (ΔPP) witnessed during expiration. Therefore, techniques that monitor beat-to-beat alterations in blood pressure in patients on mechanical ventilation and in sinus rhythm can augment the analysis of intravascular volume, an emerging technology that may expand the value of arterial pressure monitoring (20,21).

Measurement of Venous Pressures

The measurement of central venous and pulmonary venous pressure is used to estimate the right and left atrial pressure (LAP), respectively. In the absence of obstruction (e.g., superior vena cava syndrome), superior vena cava pressure (CVP) equals mean RAP which, in the absence of tricuspid valve disease, equals right ventricular end-diastolic pressure (RVEDP). Similarly, in the absence of pulmonary venous obstruction (e.g., high alveolar pressure with PEEP, pulmonary veno-occlusive disease), the pressure obtained by inflating the balloon on the end of a flow-directed pulmonary artery catheter (Fig. 3.7), referred to as the pulmonary artery occlusion pressure (PAOP) or pulmonary capillary wedge pressure (PCWP), equals mean LAP, which in the absence of mitral valve disease, equals left ventricular end diastolic pressure (LVEDP). Therefore, in most patients, CVP and PAOP measure right and left ventricular filling pressures (22). As described in section on "Ventricular Physiology," these pressures are directly proportional to EDV, provide an indirect measure of ventricular preload and still a direct measure of the pressure within the lumen of the superior vena cava and pulmonary capillaries. Ranges of normal and representative abnormal values for CVP and PAOP are shown in Table 3.8.

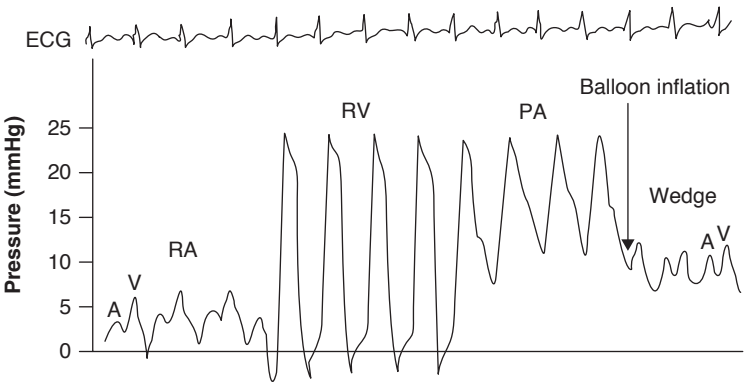

Figure 3.7 A representation of the pressure tracing as a balloon-tipped pulmonary artery catheter is passed from the right atrium, through the right ventricle, and into the pulmonary artery. Further advancement results in the "wedge" or pulmonary artery occlusion pressure wave form depicted. Note that this wave is not flat, but with atrial and ventricular contraction it exhibits an "a" and a "v" wave. *Source*: From Ref. 114.

Table 3.8 Representative Values of Venous Pressures

Condition	CVP mm Hg	LAP (PCW) mm Hg
Normovolemia	5–15	5–15
Hypovolemia	<5	<5
Heart failure	>18	>18

Abbreviations: CVP, central venous pressure; LAP, left atrial pressure; PCW, pulmonary capillary wedge.

In patients with normal cardiac function, CVP is a few mm Hg lower than LAP and PAOP is nearly identical to LAP. However, acute and chronic heart and pulmonary disease (Table 3.9) may not only interfere with the relationship of atrial pressure to ventricular end diastolic pressure, but can also make CVP and PAOP unequal, sometimes changing in opposite directions (22). Thus, in patients with known cardiac or pulmonary disease simultaneous measurement of the right and left ventricular filling pressure can be more useful and is usually achieved by placing the flow-directed pulmonary artery catheter percutaneously.

Blood Volume Measurement

As noted previously and described more fully in the section on "Confounding Variables," measurement of intraluminal pressure is an imprecise monitor of vascular volume and, in particular, cardiac preload. During the last decade, the use of transpulmonary thermodilution has been applied to measure both cardiac output (see below) as well as intrathoracic blood volume (ITBV). ITBV has been shown in populations as diverse as cardiac surgery and pancreatitis patients to have the ability to provide a better indication of cardiac preload and the potential to respond to intravascular volume augmentation than either CVP and/or PAOP measurement (23,24).

Cardiac Output Measurement

Thermodilution

Cardiac output can be easily measured using the same pulmonary artery catheter that measures pulmonary artery pressures and PAOP as well as other methods that use thermodilution. Thermodilution is based on the principle of indicator dilution with "cold" as the indicator that is injected into an unknown volume. Indicator dilution has been used for decades to measure static physiologic volumes (e.g., blood volume, extracellular fluid volume). However, since cardiac output is a time-dependent variable, time must be included in the measurement technique. For example, to measure a static volume (V) a known amount of indicator (I) can be mixed in the

Table 3.9 Disease Likely to Manifest an LAP Not = CVP

- Acute left-sided myocardial infarct
- Disease with ejection fraction <50%
- Mitral or tricuspid regurgitation
- Pulmonary embolism
- Tension pneumothorax
- Early pericardial tamponade

volume and the concentration of I (C) measured. A good scientist will determine C many times and then calculate the mean. V then equals I/mean C. In a time-dependent system, a known amount of indicator I is mixed into a time-dependent volume Q(t) and results in a time-dependent concentration C(t). The measurement of concentration of the indicator as a function of time is depicted in Figure 3.8. To calculate Q(t), the mean of the measured concentration must be determined by the mean value theorem such that:

$$\text{mean } C(t) = \frac{\text{the integral of } C(t)\ dt \text{ from time 0 to time T}}{T}$$

$$Q(t) = I/\text{mean } C(t)$$

The same concept is used with the thermodilution technique. Therefore, using an "amount" of cold injected into the right atrium that mixes with the blood in the right ventricle and pulmonary artery, the "concentration" of cold is measured by the thermistor at the end of the pulmonary artery catheter or elsewhere in the arterial system. The integration of this time-dependent concentration and division into the amount of cold is automatically accomplished by the computer supplied with the measurement equipment. The correlation between thermodilution cardiac output and indocyanine green indicator dilution is excellent (r = 0.99). The correlation of pulmonary artery catheter (PAC) thermodilution cardiac output with that obtained using the transpulmonary device (TPD) that measures ITBV is also excellent (r = 0.96) (25).

Esophageal Doppler Monitor

The esophageal Doppler probe measures the velocity of blood flow in the lumen as well as the diameter of the descending thoracic aorta. Using the shape of the velocity curve and several calculations, these data can provide information about cardiac output, preload, and systemic resistance. Placement and interpretation of data may be less challenging than PAC placement and data interpretation, but there is no information provided about pulmonary artery parameters that might influence the right heart function analysis. Several studies have supported esophageal doppler monitor (EDM) for assessing the response to intravascular volume augmentation (26–28).

Ultrasound

Echocardiography is useful for assessing ventricular function, heart valve alterations, and pericardial fluid accumulation. As a snapshot of cardiac function, echocardiography provides little assistance in the hour-to-hour, intervention-to-intervention, evaluation of response to management. Even when hemodynamic function is analyzed during the snapshot, the value of echocardiographic data has been questioned (28,29).

Ultrasound of the diameter of the inferior vena cava can be used to assess intravascular volume, an especially practical adjunct during the initial evaluation and resuscitation of a trauma patient (30,31).

Tissue Oxygen Measurement

Both near-infrared spectroscopy (NIRS) and transcutaneous pO_2 measurement show promise for identifying peripheral tissues at risk. Evidently, when peripheral tissues are at risk, vital

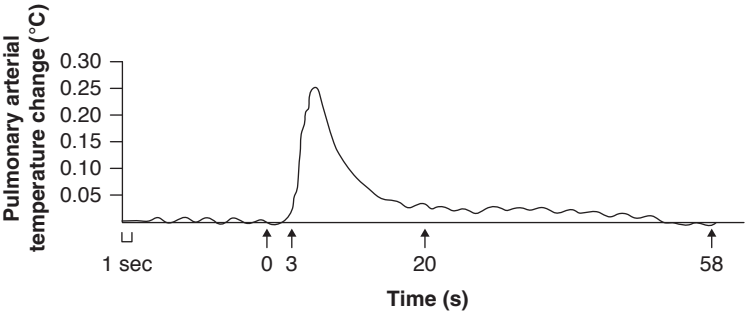

Figure 3.8 A typical indicator dilution curve, which can be used to calculate cardiac output.

organ function is also at risk despite the sacrifice of flow to less vital organs. Failure to achieve resuscitation of oxygen-related parameters as measured by either technique is associated with a poor outcome and such techniques may be more sensitive and specific than the measurement of global parameters such as cardiac index and oxygen delivery (32–34).

Measurement of Tissue pCO_2

Carbon dioxide (CO_2), along with ATP and heat, is a product of oxidative phosphorylation. As tissue perfusion brings oxygen to cells, it takes CO_2 away. As the lungs serve to add oxygen to the blood, they serve to remove CO_2. Decreased tissue perfusion results in CO_2 tissue accumulation and decreased lung elimination from increased physiologic dead space (see chap. 6). Anaerobic metabolism results in lactic acid production and subsequent interaction with the bicarbonate buffer that can also increase tissue CO_2 (35). Therefore, tissue CO_2 accumulation and the difference between tissue pCO_2 ($tpCO_2$) and arterial pCO_2 ($apCO_2$) are markers of both perfusion and metabolic deficits in the monitored tissue.

Gastrointestinal tract (GIT) perfusion is particularly vulnerable to the neuroendocrine response to decreased cardiac output (see chap. 8) and an increase in tissue pCO_2 during critical illness has been documented even in the stomach, a portion of the GIT with robust arterial supply. Data in humans support the concept that upper intestinal tissue pCO_2 is a practical marker for the magnitude of shock and the response or lack of response to therapy (36,37).

Measurement of stomach pCO_2 has methodological difficulties and emerging technologies are assessing the use of pCO_2 monitoring at sublingual, buccal, and urinary bladder sites (38–40). Tissues in the facial region and pelvis are usually considered less threatened by the neuroendocrine response to hypoperfusion as compared to the GIT, but sublingual and urinary bladder data suggest vulnerability equal to that in the proximal GIT (39,40).

Measurement of Oxygen Delivery (DO_2) and Consumption (VO_2)

Placement of a pulmonary artery catheter not only allows measurement of cardiac output, but also of mixed venous blood gases, which along with arterial blood gases and hemoglobin, allow for calculation of DO_2 and VO_2 (Table 3.2). Since many disease states either diminish oxygen delivery and/or increase oxygen consumption (see chap. 2), a plot of the relationship between delivery and consumption may be a more useful indication of the need for further hemodynamic interventions than the absolute DO_2 and VO_2 values, per se (see Fig. 2.1). Optimization of oxygen delivery may be considered present when an increase in DO_2 results in no further increase in VO_2 (supply-independent oxygen consumption). This concept has resulted in considerable controversy in patient management (see below).

Measurement of Central Venous or Mixed Venous Oxygen Saturation

Measurement of DO_2 and VO_2 requires more invasive equipment (PAC) and/or more sophisticated oxygen monitoring (measurement of oxygen consumption in the ventilation circuit)

than are commonly used in critical care units today. Mixed venous saturation (mvO_2 sat) has been shown to have a direct relationship to the ratio of DO_2 to VO_2 with an r value of 0.96 (41). Normal mvO_2 sat is >70%, indicating that no more than 30% of DO_2 is utilized in healthy, baseline states. Studies of oxygen delivery and consumption during critical illness suggest that supply independent oxygen consumption is also achieved when mvO_2 sat has reached this concentration, with the implication that further efforts to improve DO_2 are not warranted (see chap. 2).

Since measurement of mvO_2 sat necessitates a PAC, the use of central venous oxygen saturation (cvO_2 sat) has been advocated as a surrogate for mvO_2 sat, especially since this appeared to be a good indicator of successful resuscitation in severe sepsis (42). Many studies before and since the publication of this resuscitation paradigm have indicated an imperfect correlation between mvO_2 sat and cvO_2 sat, especially in patients with a low cardiac index (43). Typically, cvO_2 sat is several percentage points higher than mvO_2 sat. Although imperfect, if empiric data show that cvO_2 sat >70% is associated with a reduction in morbidity and/or mortality, then the practical value of this measure of total body tissue oxygenation is evident.

Acid–Base Monitoring

Acid–base monitoring during surgical critical illness is commonly employed by measurement of arterial pH, base-deficit calculations, and measurement of lactic acid. Of these, arterial pH, which can be influenced by ventilation as well as various cellular metabolic states, is the least useful. Base deficit is more specific for metabolic alterations, but is influenced by high concentrations of chloride provided with 0.9% saline infusion (44,45). Lactic acid, then, is the preferred monitor and, certainly, lactic acid concentrations have been linked to oxygen delivery deficits and oxygen debt (see chap. 2). Since metabolic alterations that impair pyruvate metabolism without hypoxia can also increase lactic acid concentrations, a more specific indication of anaerobic lactic acid production is an increase in the lactate–pyruvate ratio, a value that is typically unavailable in common clinical laboratories. At present, an increase in lactic acid, therefore, infers a poor prognosis and can also infer an oxygen delivery deficit, but this variable should not be the only monitor driving hemodynamic management decisions (46,47).

CONFOUNDING VARIABLES

Each of the hemodynamic monitors described above can provide misleading information because of improper technique, inadequate experience with the device, or because of physiologic changes that make the information difficult to interpret. This section will cover the common confounding variables in hemodynamic monitoring and suggest methods to diminish confusion.

Physical Examination

In surgical critical illness, physical examination and other clinical information is often inadequate to predict measured hemodynamic variables (48). For instance, a common error is to misinterpret the physical examination information suggesting total body salt and water excess (evidence of peripheral and pulmonary edema and weight gain) as evidence that intravascular volume is in excess (i.e., that this indicates CHF). Therefore, other monitoring techniques are often used to assess the circulation. Unfortunately, just like physical examination, these tools are not immune from artifacts or misinterpretation.

Arterial Pressure Monitoring

As mentioned previously, severe peripheral vasoconstriction may lower pressures measured in the radial or dorsalis pedis arteries as compared to pressures measured in the femoral or more proximal vessels. Even if the more proximal pressure is higher, vasoconstriction of this magnitude usually denotes hypoperfusion worthy of intervention.

Such physiological reasons for a significant discrepancy between aortic pressure and more peripheral pressures are rare and a normal arterial pressure tracing is sufficiently well

Table 3.10 Confounding Variables in Venous Pressure Monitoring

Central venous pressure
1. Improper position
2. Inadequate wave form
3. Changing right ventricular compliance
   A. Afterload
   B. Ischemia
   C. Tension pneumothorax
   D. PEEP
   E. Tamponade
4. Increased intrathoracic pressure
   A. PEEP
   B. Tension pneumothorax
   C. Increased abdominal pressure

Pulmonary artery occlusion pressure
1. Improper placement
   A. Right ventricle
   B. Too peripheral
   C. Lung zones I and II
2. Inadequate wave form
3. Changes in left ventricular compliance
   A. Afterload
   B. Ischemia
   C. Ventricular filling
   D. Tamponade
   E. Hypovolemia
   F. PEEP
4. Increased thoracic pressure
   A. PEEP
   B. Tension pneumothorax
   C. Increase abdominal pressure

understood that artifactual alterations in a pressure tracing (e.g., plugged catheter, position related dampening of the signal, etc.) are usually readily recognized by the critical care team.

Venous Pressure Monitoring (Table 3.10)

In contrast to arterial pressure monitoring, venous pressure monitoring (central venous, pulmonary venous, right atrial, left atrial) is subject to many confounding variables, including the lack of recognition of proper wave form, disregard for unphysiologic relationship between monitored variables, diminished ventricular compliance, and increased intrathoracic pressure.

Lack of Recognition of Proper Wave Form

A normal right and LAP tracing demonstrates an increase in pressure corresponding to atrial contraction (A wave) followed by a second increase secondary to ventricular contraction (V wave) (Fig. 3.9). Catheters placed in the large thoracic veins and the occluded pulmonary artery should also demonstrate this picture, although commonly with some damping as compared to atrial placement. CVP, LAP, and PAOP should not be flat lines. With the loss of atrial contraction (atrial fibrillation, junctional rhythm), only the V wave, timed with ventricular contraction, will be recognized.

If a flat line is monitored, the catheter may not be providing proper information. This is most likely to occur with overinflation of the pulmonary artery catheter balloon ("over-wedging") that can also result in a falsely high number (Fig. 3.10).

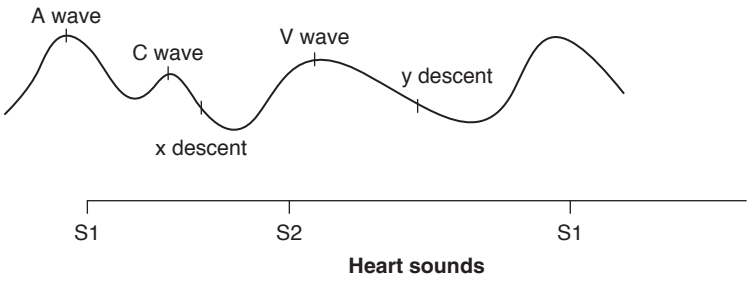

Figure 3.9 Schematic representation of the prominent "a" and "v" waves of pulmonary artery occlusion tracings, which are characteristic of the presence of atrial contraction along with ventricular contraction.

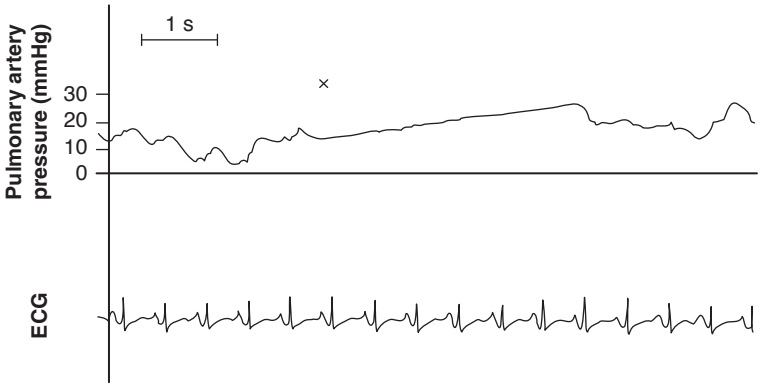

Figure 3.10 A representation of the effect of overinflation of the pulmonary artery catheter balloon on the pressure tracing. Characteristically, the pressure increases.

Confirmation that the balloon-inflated PA catheter tip is in proper position can be obtained by aspirating blood and obtaining a blood gas. If the aspirated blood meets all three criteria listed in Table 3.11, the PAOP is most likely accurate (49).

Disregard for Unphysiologic Relationship Between Monitored Variables

As stated under section on "Ventricular Physiology," in patients with normal or good ventricular function (ejection fraction ≥50%), the CVP, LAP, and PAOP are similar, if not equal. Patients with large discrepancies between right and LAP should have evidence of previous or acute right or left ventricular dysfunction. Otherwise, the mechanics of the monitoring system (e.g., transducer levels, calibration, line placement, etc.) should be checked.

When pulmonary artery pressure is monitored, the mean PAP should be at least 8 mm Hg greater than the PAOP. When the PAOP is 8–10 mm Hg lower than the PAP, the pulmonary artery diastolic pressure (PAD) will equal the PAOP. As mentioned previously under Vascular Resistance, disease processes increase pulmonary vascular resistance, thus elevating PAP and PAD more than PAOP. It is unphysiologic, therefore, to record a PAP of 25 mm Hg and a PAOP of 22 mm Hg. Most often, this occurs because of poor recognition of the proper PAOP wave form and "over-wedging" of the balloon catheter. However, a PAP of 30 mm Hg with a PAD of 20 and a PAOP of 12 mm Hg can represent evidence of increased pulmonary vascular resistance without an increase in left ventricular filling pressure. Using the PAD as a measure of ventricular filling pressure may be inaccurate in many disease states that increase pulmonary vascular resistance.

Table 3.11 Confirmation of Proper Location for Pulmonary Artery Occlusion Pressure (Aspiration of Blood from Occluded Catheter)

- PAOP O_2 - PaO_2 ≥19 mm Hg
- $PaCO_2$ - PAOP PCO_2 ≥11 mm Hg
- pH PAOP - PHA ≥0.08
- PAOP arterial saturation >95%

Diminished Ventricular Compliance

As described in section on "Ventricular Physiology," ventricular filling pressures are used as an indirect measure of ventricular volumes. The relationship between pressure and volume (compliance) is changed by various mechanisms (Table 3.10). When compliance is diminished, little preload (EDV) may result in a normal or elevated pressure. Under these circumstances, an elevated pressure may not indicate overstretched myocardium (a mechanism of heart failure) and measures used to reduce volume (diuretics) may aggravate hypoperfusion. Therapy should be provided to improve compliance, which frequently results in better perfusion at lower pressures (i.e., afterload reduction with vasodilator therapy, pericardiocentesis).

Increased Intrathoracic Pressure

Intrathoracic pressure may increase because of increased pressures required for ventilation (especially with PEEP), tension pneumothorax, or increased abdominal pressure. Irrespective of the cause, hemodynamic monitoring devices placed in the thorax will be affected by the extraluminal increase in pressure and record a pressure that represents the sum of intraluminal and extraluminal forces. The transmural pressure (intraluminal pressure – extraluminal pressure) is recognized as a more physiologic measure of atrial and ventricular end-diastolic pressures.

Despite the development of a balloon-equipped nasogastric tube for the measurement of esophageal pressure, there has been little investigation in humans using equipment to measure the extraluminal pressure that might be applied to the intraluminal pressure monitoring devices (50). The use of esophageal pressure monitoring for ventilator management (see chap. 6), may result in renewed interest in this monitoring adjunct (51).

For CVP and PAOP measurement, calculation of the transmural pressure by using an esophageal pressure monitor may more accurately reflect ventricular end-diastolic pressure and ventricular filling. However, venous return physiology is influenced by both the intraluminal and extraluminal determinants of CVP. Therefore, an elevated CVP from an increase in intrathoracic pressure is just as detrimental to venous return as an increase from an overstretched right ventricle.

In addition to extraluminal effects, PEEP may produce intraluminal alterations in hemodynamic monitoring. For PAOP to equal LAP, a continuous column of fluid is required between the pulmonary artery segment occluded by the balloon and the left atrium. Because the PA catheter is flow directed, the PA catheter tip often locates in an area of lung that is well perfused and the continuous column achieved. The lung has been divided into the following three zones dependent on the relationship of ventilation (V) to perfusion (P): Zone I V > P, Zone II V = P, and Zone III V < P. Most often, PA catheters locate in Zone III. Increased ventilation pressures and diminished cardiac output increase the proportion of Zones I+II to Zone III. Several studies have measured a false elevation in PAOP when PEEP is applied. However, with the PA catheter tip in Zone III, little discrepancy can be demonstrated (52).

Cardiac Output Measurement

The factors that can result in faulty cardiac output measurements using thermodilution are listed in Table 3.12. The most common reason for unsatisfactory cardiac output measurement (variability of >10% in measurements taken within 5 minutes) is inconsistency in the speed of injection. A fast injection results in a lower cardiac output (less dilution volume) than a slow

Table 3.12 Factors Affecting Accuracy of Pulmonary Artery Catheter Cardiac Output Measurement

- Technique of injection
- Location of proximal port
- Low cardiac output

injection. If the proximal injection port is near a venous dilator device used for percutaneous insertion, the flow of the injectate may be partially obstructed, resulting in large variations. With cardiac outputs less than 3.5 L/min, and especially less than 2.5 L/min, the thermodilution cardiac output may overestimate the simultaneously obtained Fick cardiac output by 35%.

Variables that can influence the accuracy of esophageal Doppler measurement of cardiac output include interference from a nasogastric tube, high PEEP, poor signal quality and stability, and inadequate sedation (27).

Urine Output

Urine output may be influenced by physiologic and nonphysiologic variables independent from renal perfusion and glomerular filtration. Osmotic substances such as glucose (commonly excreted in critical illness), vascular contrast agents, and mannitol can be the reason for a well maintained urine output despite poor renal perfusion. Since excellent renal perfusion and the resultant urine output should not result in concentrated urine, a high urine specific gravity (>1.020) should raise the suspicion of increased osmolality as the cause of urine output >0.5 $cm^3/kg/hr$ in a critically ill patient. Similarly, a diuretic can result in increased urine output despite poor renal perfusion. This is beneficial when CHF is the etiology of poor perfusion, but can be detrimental when hypovolemia is the cause.

Lactic Acid

As mentioned above, an increase in lactic acid is not absolutely specific for either global or regional deficits in oxygen delivery. In addition to inflammation induced alterations in cellular metabolism, lactic acid can be elevated from conditions that increase NADH production (alcohol intoxication, keto-acidosis).

Complications

Arterial Lines

The complications of arterial line insertion are listed in Table 3.13. The most serious one is ischemia in all or part of the hand following radial artery catheterization. Before performing radial artery, catheterization adequacy of collateral circulation can be assessed with a properly performed Allen test.

Venous Lines

The complications of central venous and pulmonary artery catheters are listed in Table 3.14. Certainly, the most immediately life-threatening complications are right ventricular arrhythmias and pulmonary hemorrhage, both associated with PAC insertion. Arrhythmias can usually be controlled with the administration of lidocaine or removal of the catheter from the right ventricle. Pulmonary hemorrhage is secondary to rupture of a pulmonary artery or branch from balloon inflation and is seen most often in at-risk patients as listed in Table 3.14. Hemoptysis, even of small quantities, may herald this potentially fatal complication. Suspicion of injury may be confirmed by radiographic demonstration of an infiltrate distal to the catheter tip. In case of severe hemoptysis, the patient should be placed in the lateral decubitus position, which places the injured lung down, and preparations should be made for the possibility of emergency pulmonary lobectomy or pneumonectomy. Alternatively, trans-PA catheter occlusion of the ruptured vessel has been used with success (53). With this potentially fatal complication in mind, the staff inflating the balloon should use gentle, slow pressure. To

Table 3.13 Complications of Arterial Catheterization

- Ischemia
- Infection
- Pseudoaneurysm
- Bleeding

Table 3.14 Complications of Venous Lines

1. Central venous and pulmonary artery lines
   - Pneumothorax
   - Line infection
   - Hemothorax
   - Tamponade
   - Pleural effusion
   - Central venous thrombosis
2. Pulmonary artery
   - Arrhythmias
   - Endocarditis
   - Pulmonary infarct
   - Rupture pulmonary artery
     – Pulmonary hypertension
     – Mitral valve disease
     – Old age
     – Anticoagulation
     – Hypothermia

diminish inflation in small branches, the catheter tip should be positioned in the proximal right or left pulmonary artery.

Indications for Hemodynamic Monitoring

Arterial Lines

The indications for intraoperative and postoperative arterial line insertion are listed in Table 3.15. Many anesthesiologists consider constant blood pressure and frequent arterial blood gas determinations essential to proper intraoperative management of patients undergoing major procedures. The new cardiac output and ITBV measurement devices use an arterial line. However, the potential for serious complications must be recognized and arterial line insertion should not be simply a matter of convenience.

Venous Lines

The indications for central venous and pulmonary artery (PA) catheter placement are listed in Table 3.16. Considering hemodynamic monitoring, PA catheters can be valuable when measurement of PAOP, cardiac output, pulmonary artery pressure and resistance, as well as mixed venous blood gases is essential for appropriate hemodynamic diagnosis and therapy. As previously mentioned, patients with ventricular ejection fractions >50% are expected to demonstrate that CVP, PAOP, and LAP are very similar (50). Therefore, in patients with good cardiac function and no history of heart disease, CVP should be an adequate measure of atrial pressures. More difficult to assess is the usefulness of PA catheters in patients with significant heart disease, such as that listed in Goldman's classification (Tables 3.17 and 3.18). This and similar classifications relate to the risk of a coronary event (i.e., myocardial infarction) in patients with known heart disease as well as other life-threatening cardiac complications. The use of PA catheters and rigorous hemodynamic management for patients considered at high risk of a postoperative coronary event has been effective in reducing perioperative infarction. In addition,

patients in Goldman's Class IV are more likely to demonstrate unequal atrial pressures and require cardiovascular drug manipulations during any major operation or illness. PAC placement in this group may greatly help in distinguishing etiologies of poor perfusion and response to therapy, although the effect of PAC use on the eventual outcome in these patients is controversial. The potential hemodynamic benefit of PAC monitoring in Class III patients is more difficult to assess, but seems warranted in patients suffering severe insults (severe septic shock, multiple trauma) or with pre-existing disease likely to produce major fluid shifts (chronic renal failure requiring dialysis). Each case should be individualized with recognition that certain patients may benefit because of known impairment of the circulation as well as the risk of severe impairment, which can result from disease or surgical intervention (54–58).

Table 3.15 Indications for Arterial Line Placement

- Arterial pressure monitoring
- Arterial blood gas monitoring
- Access for frequent blood tests
- Thermodilution cardiac output
- Measurement of ITBV

Table 3.16 Indications for Central Venous and Pulmonary Artery Catheter Placement

Central venous line
- Hemodynamic monitoring
- Venous access for fluid administration
- Total parenteral nutrition
- Administration of cardiovascular drugs

Pulmonary artery catheter placement
- Hemodynamic monitoring
- Administration of cardiovascular drugs

Table 3.17 Goldman Cardiac Risk Index Cardiac Complication Risk

Clinical Factor	Points
S3 Gallop or JVD on preoperative examination	11
Myocardial infarction within 6 months	10
Premature ventricular beats, more than 5/min, documented anytime (patients with known heart disease)	7
Rhythm other than sinus or premature atrial contractions on last preoperative EKG	7
Age >70 years	5
Emergency operation	4
Intrathoracic, intraperitoneal, or aortic site of surgery	3
Important valvular aortic stenosis	3
Poor general medical condition	3

Table 3.18 Hemodynamic Class (Goldman)

Class	Points
I	0–5
II	6–12
III	13–25
IV	≥26

Esophageal Doppler

Much of the data illustrating the value of using EDM has been gathered during surgery, using EDM to guide fluid management. Therefore, this monitor may be particularly valuable for high-risk patients undergoing extensive or long duration surgery (26–28).

Cardiovascular Drugs

Vasopressor Agents (Table 3.19)

Vasopressor drugs are principally employed to increase arterial pressure. Phenylephrine is an α_1 receptor agonist that causes arterial vasoconstriction with little, if any, other cardiovascular effect. Likewise, vasopressin is a potent vasoconstrictor (V_1-receptor mediated), principally of resistance vessels throughout the circulation. The GIT, coronary, and brain circulations are particularly affected. Hypovolemia and hypotension are a more potent stimulant to endogenous vasopressin release than hyperosmolality. Therefore, vasopressin secretion will continue in the face of a hypo-osmolar state if the circulatory disturbance persists. Norepinephrine engages α_1, α_2, and β_1 receptors and causes principally an increase in blood pressure by increasing vascular resistance rather than an increase in cardiac output. In higher doses (20 µg/kg/min range), dopamine can affect α_1 receptors and increase peripheral resistance. Compared with norepinephrine, dopamine administration is associated with higher oxygen consumption as a pharmacologic effect. Vasopressin infusion does not appear to influence oxygen consumption in the setting of acute lung injury (59– 61).

Inotropic Agents (Table 3.20)

Myocardial contraction depends on the action during systole of increased intracellular calcium on the contractile proteins actin and myosin. Cyclic AMP, which alters intracellular calcium flux, can increase calcium concentration during systole and increase the inotropic state. Most inotropic agents either increase intracellular calcium (action of digitalis), or increase cyclic AMP by stimulation (Beta-Adrenergic Agonists - Dopamine and Dobutamine) or phosphodiesterase inhibition. In general, positive inotropic agents increase cardiac contractility and produce an upward and leftward shift of the cardiac function curve (Fig. 3.4). All drugs that increase contractility and/or heart rate will increase the total body oxygen consumption. Therefore, it is difficult to discern a principle effect on cell energetics when these drugs are employed (62).

For the treatment of CHF or cardiogenic shock, reduction in afterload will often result in additional improvement in cardiac function. While vasodilator drugs are commonly used to reduce afterload and preload, several of the positive inotropic drugs have beneficial actions on the vasculature. Table 3.20 lists the relative hemodynamic actions of the commonly used inotro-

Table 3.19 Hemodynamic Effect of Vasopressor Drugs

Drug	CO	HR	SVR
Phenylephrine	NC or DEC	NC	INC
Norepinephrine	±	NC	INC
Vasopressin	NC	NC	INC

Abbreviations: NC = no change; DEC = decrease; INC = increase.

Table 3.20 Hemodynamic Effects of Positive Inotropic Agents

Drug	Cardiac Output Rate	Preload	Heart	Systemic Vascular Resistance
Digitalis	+ INC	+ DEC	+ DEC	±
Dopamine	++ INC	+ INC	++ INC	+ INC
Dobutamine	++ INC	++ DEC	+ INC	+ DEC
Amrinone	++ INC	++ DEC	±	+ DEC
Milrinone	++ INC	++ DEC	±	+ DEC

Abbreviations: INC = increase; DEC = decrease.

pic agents. Of particular importance is the elevation in preload documented with the use of dopamine, even in renal doses. The mechanism for this phenomenon is unclear, but argues that dopamine is not preferable in patients with high normal or elevated atrial pressures (cardiogenic states) but may be more useful in hypovolemic states (63).

Vasodilator Therapy

Vasodilator therapy may improve cardiac function by reducing afterload and/or preload. The combination of a positive inotropic drug and a vasodilator may further augment cardiac function (Fig. 3.5). The relative hemodynamic effects of commonly used vasodilators are listed in Table 3.21.

Diuretics

Diuretics are used to reduce preload and improve cardiac output by moving preload from the downward side of the cardiac function curve to the up side (Fig. 3.2). As is emphasized later, the major benefit of diuretic therapy in CHF is the improvement in cardiac output, which improves oxygen delivery. The disappearance of lung water, which follows lowering pulmonary capillary pressure, is of secondary importance.

HYPOPERFUSION STATES

The Pathophysiology of Hypoperfusion

Global and/or regional hypoperfusion is the primary mechanism responsible for inadequate oxygen delivery, and the immediate effects of hypoperfusion on cell viability are secondary to interruption of oxidative metabolism. However, as described in more detail below and in the Inflammation chapter, the pathophysiologic response to hypoperfusion and subsequent resuscitation can result in cellular and organ function alterations that may or may not be directly linked to disruption in oxidative metabolism.

The Neurohumoral Response to Hypoperfusion

Total body hypoperfusion usually manifests as a reduction in cardiac output. The most frequently studied models of total body hypoperfusion cause a reduction in cardiac output from loss of volume (hypovolemic hypoperfusion) or loss of cardiac function (cardiogenic hypoperfusion). Either of these two etiologies may result in the neurohumoral response listed in Table 3.22.

The readily apparent clinical effects of this neurohumoral response is tachycardia (epinephrine, norepinephrine, dopamine), vasoconstriction (norepinephrine, arginine vasopressin - AVP, angiotensin), diaphoresis (norepinephrine), oliguria with sodium and water conservation (adrenocortical trophic hormone - ACTH, cortisol, aldosterone, AVP), and hyperglycemia (epinephrine, glucagon, cortisol, decreased insulin). This activation of the neuroendocrine system may preserve blood flow to vital organs (heart, lungs, brain) while diminishing flow to less vital organs (kidneys, gastrointestinal tract, skin, muscle), and serves to preserve intravascular volume by limiting urine output. This response is more homeostatic under conditions of hypovolemic hypoperfusion compared to cardiogenic hypoperfusion where tachycardia, vasoconstriction, and sodium and water retention may aggravate rather than diminish hypoperfusion (see discussion below on cardiogenic states).

Table 3.21 Hemodynamic Effects of Vasodilators

Drug	Preload	Afterload
Nitroglycerin	+++ DEC	+ DEC
Nitroprusside	+++ DEC	+++ DEC
Calcium channel blocker	+ DEC	+++ DEC

Abbreviations: DEC = decrease.

Effects of Hypoperfusion on Inflammation (Hypoperfusion Begets Inflammation)

While several mechanisms associate hypoperfusion insults with an inflammatory response (Table 3.23), the most clearly documented association of hypoperfusion with inflammation is the effect of ischemia followed by reperfusion. Clinically, this is most obvious in cases of isolated limb ischemia (compartment syndrome) and in some cases of localized intestinal ischemia. However, severe systemic hypoperfusion may result in a similar response in many tissues, particularly the GIT.

The mechanism responsible for ischemia reperfusion injury appears to require both local and systemic factors. A complex interaction of oxygen free radicals, thromboxane, leukotrienes, phospholipase A2, nitric oxide, intracellular calcium accumulation, and leukocytes participate in both regional and total body alterations in capillary permeability, cell injury, and organ function (64). Anatomical and physiological damage to the intestine, limb, kidney, liver, and lung may follow reperfusion even when a specific organ (i.e., lung) was not initially hypoperfused. Since polymorphonuclear leukocytes - PMNs are potent producers of oxygen-free radicals, these cells are central to this pathophysiology.

The potential for severe inflammation to develop during rather than following hypoperfusion and reduced oxygen delivery has accrued progressive documentation (65–71).

In clinical hypoperfusion, particularly with trauma, it is difficult to separate tissue injury secondary only to hypoperfusion from damage from other mechanisms, such as a direct blow. Again, irrespective of the cause, hypoperfusion and inflammation commonly occur together. This combination is particularly prone to result in organ malfunction and/or death.

Clinical Diagnosis of Hypoperfusion

The fundamentals of resuscitation demand attention to the airway (A), breathing (B), and circulation (C). The presence or absence of an adequate airway is not usually difficult to ascertain. Clinical examination, chest X-rays, and arterial blood gases are often sufficient to determine whether breathing is adequate to support tissue oxygenation and carbon dioxide elimination. However, the diagnosis of an adequate or inadequate circulation is often more difficult to discern when principally based on clinical examination and simple tests.

Table 3.22 Neurohumoral Response to Hypoperfusion

Increased	Decreased
Epinephrine	Insulin
Norepinephrine	Thyroxine
Dopamine	Triiodothyronine
Glucagon	Luteinizing hormone
Renin	Testosterone
Angiotensin	Estrogen
Arginine vasopressin	Follicle-stimulating hormone
ACTH	
Cortisol	
Aldosterone	
Growth hormone	

Table 3.23 Hypoperfusion Begets Inflammation

I. Hypoxia stimulates an inflammatory response
II. Cytokine activation during hemorrhage
III. Ischemia/reperfusion
IV. Tissue necrosis
V. Gastrointestinal tract translocation

Despite these limitations, the first step in clinical evaluation of the circulation is to examine the patient. Usually, an abnormality noted on physical exam (e.g., hypothermia, hypotension, tachycardia, pale and/or cool extremities, altered mental status, decreased urine output) is sufficient evidence of a poor circulation (Ebb Phase of Shock; see chap. 2) and should initiate therapy and further study. Unfortunately, clinical and experimental studies suggest that cell damaging circulation deficits (within the macrocirculation, microcirculation, or both) may be present with little or no obvious clinical alterations. Thus, as described above, several additional tools have been advocated to assess the circulation, ranging from simple to invasive (Table 3.24).

Evidence of Metabolic Acidosis

The long understood effects of anaerobic metabolism on the Krebs cycle and the glycolytic pathway has resulted in the assumption that elevated plasma or serum lactic acid is a specific indication of anaerobic metabolism secondary to inadequate oxygen supply to either the entire body (i.e., hemorrhagic hypoperfusion) or regions of the body (i.e., embolism to the superior mesenteric artery).

In critical illness, however, anaerobic metabolism is not the only influence on lactate production. For instance, during severe inflammation, lactate levels may increase secondary to effects on cellular metabolism (e.g., increased glucose metabolism, decreased pyruvate dehydrogenase activity, effects of nitric oxide), which do not require anaerobic conditions (see chap. 2) (72–74).

Regardless of the etiology, persistent metabolic acidosis and elevated lactic acid are associated with poor outcomes in surgical critical illness (73,74). Recognition of a metabolic acidosis, therefore, should serve as a stimulus to search for a reversible process and, thus, possibly affect outcome. When metabolic acidosis is recognized along with an elevated lactic acid, does this mean the patient suffers solely from lack of oxygen delivery or does a component of severe inflammation also contribute to the degree of illness and potential for a poor outcome? Again, the astute clinician should consider and address both possibilities.

Evaluation of DO_2 and VO_2

As described in the monitoring section above, mixed venous oxygen saturation (mvO_2sat) is directly proportional to the ratio of DO_2/VO_2, and values >70% usually indicate that VO_2 is not

Table 3.24 Adjuncts for Evaluation of the Circulation

- Evidence of metabolic acidosis
  - Increased lactic acid
  - Increased base deficit
- Evaluation of systemic oxygen delivery and consumption
  - Direct measurement of delivery and consumption
  - Indirect measurement of delivery and consumption
  - Measurement of mixed venous oxygen saturation
  - Measurement of central venous oxygen saturation
  - Measurement of tissue oxygen concentration
- Measurement of tissue pCO_2
  - Gastric
  - Sub-lingual
  - Buccal
  - Urinary bladder
- Additional monitors of metabolic deficits
  - Hypothermia
  - Hyperglycemia
  - Decreased ionized calcium
  - Hypokalemia in trauma

delivery dependent. Central venous oxygen saturation (cvO_2 sat) has been used as a substitute for mvO_2 sat. With either monitor, a high venous saturation (>70%) noted together with an increased lactic acid and other variables such as hypothermia would support a diagnosis of shock in the Ebb Phase, whereby providing more oxygen delivery would not likely improve outcome. In contrast, a low venous saturation (<65%) associated with metabolic acidosis and hypothermia would suggest shock in the Ebb Phase with the possibility of improving consumption following increased delivery and, hence, the importance of making an accurate diagnosis of the etiology of hypoperfusion. Achievement of venous saturations >70% as well as resolution of an elevated lactic acid and hypothermia would be consistent with migration from the Ebb Phase to the Flow Phase and improved survival probability (42).

More complicated consideration of DO_2 and VO_2 demands the use of a PAC or other methods of measuring delivery and consumption. In surgical critical illness, particularly after resuscitation from hypoperfusion and with severe inflammation, DO_2 and VO_2 usually increase as compared to basal states (Flow Phase; see chap. 2). Many authors argue that the VO_2/DO_2 dependency curve shifts up and to the right, increasing the magnitude of delivery-dependent VO_2 and accentuating the possibility of tissues suffering from inadequate oxygen delivery (see Fig. 4.2). Using this logic, adequate resuscitation of the circulation demands that DO_2 be increased until VO_2 no longer increases (often achieved when the values listed in Table 3.25 are realized). This has been termed supply-independent oxygen consumption.

Several authors have documented difficulties in achieving supply independent oxygen consumption. Some studies have also demonstrated excellent tissue oxygen levels during severe inflammation that argue against inadequate oxygen delivery as a primary process of cell injury (75,76).

Despite such differences in published information, several important generalizations can be gleaned from the large amount of data gathered in these reports.

Patients who have increased cardiac index, oxygen delivery, and consumption in response to usual methods of resuscitation of the circulation (i.e., infusion of fluids and red cells) tend to survive, especially when the increase in these parameters approaches or meets the hyperdynamic values, as shown in Table 3.25 (Flow Phase) (77).

Patients who do not achieve a hypermetabolic state (particularly no increase in oxygen consumption) during critical illness, with or without the infusion of inotropic and vasopressor agents, are more likely to develop organ failure or succumb (continuation of the Ebb Phase) (77–81).

As mentioned in the monitoring section above, the administration of drugs that increase heart rate and contractility (particularly a β agonist) can result in an increase in total body oxygen consumption. This along with the possibility of methodological linkage in the calculation of oxygen delivery and consumption have stimulated concern that much of the oxygen data gathered in such trials as those referenced above are inaccurate measures of cell metabolic response (82). However, the common theme in these studies is that a lack of response to hemodynamic manipulation is most evident by no increase in total body oxygen consumption. Therefore, even if the augmentation in oxygen utilization stimulated by these therapeutic interventions is secondary to drug effect, the cells that do not respond to these maneuvers indicate a continuing deficit in cellular metabolism, that is, a rude unhinging of the machinery of life most indicative of continuing shock (see chap. 2). Such a deficit indicates the inability of cell energetics to migrate from the Ebb Phase to the Flow Phase of shock, a marker for a high mortality risk.

Table 3.25 Nonstressed vs. the "Ideal" Hyperdynamic State

Parameter	Nonstressed	Ideal
Cardiac index	2.5–3.5 L/min/M^2	>4.5 L/min/M^2
Oxygen delivery	400 mL/min/M^2	>600 mL/min/M^2
Oxygen consumption	130 mL/min/M^2	>170 mL/min/M^2

Decreased Ionized Calcium

Ionized calcium is now frequently measured with arterial blood gas analyzers and, therefore, can be regularly monitored. Ionized calcium decreases with hemorrhagic hypoperfusion, during resuscitation for cardiac arrest, and during severe inflammation. Commonly, this decrease is coincident with a metabolic acidosis that would by itself increase blood ionized calcium. Mortality is higher in patients who arrive in a critical care setting with low ionized calcium.

The etiology of this phenomenon is debated, but does not appear to be secondary to inadequate parathormone (PTH) secretion or extracellular sequestration. Several studies have suggested that intracellular migration of calcium is the etiology and reflective of alterations in cellular membrane function during critical illness (83–86).

Therefore, decreased ionized calcium without a clear etiology (such as elevated phosphate or decreased magnesium) may indicate ongoing hypoperfusion and/or inflammation.

ETIOLOGIES OF HYPOPERFUSION (TABLE 3.26)

Decreased Venous Return

Hypovolemia

Hypovolemia is the most common etiology of decreased venous return secondary to decreased MCFP. Common etiologies of hypovolemia are listed in Table 3.27.

Severe hypoperfusion secondary to hypovolemia, hypovolemic shock, has been studied most frequently in experimental and clinical hemorrhage. Hemorrhagic shock not only diminishes venous return, but also may produce cardiovascular alterations as listed in Table 3.28 (87,88). Cellular effects (other than lactic acidosis from anaerobic glycolysis) that have been described are listed in Table 3.29. As mentioned above, ischemia-induced local and systemic inflammation has also been described.

Table 3.26 Etiologies of Hypoperfusion

1. Decreased venous return
   - Hypovolemia
   - Pericardial tamponade
   - Tension pneumothorax
   - Increased abdominal pressure
     Bowel obstruction
     Tension pneumoperitoneum
     Massive bleeding
     Diagnostic laparoscopy
     Pneumatic antishock garment
     Ascites
   - PEEP
2. Decreased myocardial function
   - Congestive heart failure
   - Cardiogenic shock

Table 3.27 Common Etiologies of Hypovolemia

Hemorrhage
Severe inflammation/infection
Burns
Trauma
Excess diuresis
Vomiting
Bowel obstruction
Pancreatitis
Inadequate oral intake
Peritonitis

The metabolic and/or toxic phenomena associated with hypovolemic shock, even without severe inflammation, result in the loss of plasma and interstitial volume beyond that which can be accounted for by the primary disease process (i.e., hemorrhage, vomiting), with migration of interstitial fluid into cells and increased capillary permeability implicated as mechanisms (89).

Physical Examination in Hypovolemic Hypoperfusion

The hypovolemic patient will exhibit vital signs and physical examination evidence of hypoperfusion roughly in proportion to the degree of hypovolemia. A 10% loss of plasma volume (560 cm^3, about the amount donated for transfusion) produces little, if any, disturbance. A 20% loss may result in tachycardia and orthostatic hypotension. A 30% loss may produce hypotension while supine. However, a patient may be normotensive when supine even with greater loss of plasma volume.

Agitation, tachypnea, and peripheral vasoconstriction commonly accompany all significant degrees of hypovolemia. Warm extremities may be seen in inflammation despite hypovolemia and may also be present following spinal cord injury and anaphylaxis.

Neck veins will not be distended unless hypovolemia is accompanied by an extracardiac increase in pressure (tension pneumothorax, pericardial tamponade, severe effort during expiration, increased abdominal pressure). An S3 gallop will not be present. An etiology of hypovolemia may also be apparent (open wound with hemorrhage, distended abdomen, femur and pelvic fractures).

Agitation, tachypnea, and peripheral vasoconstriction are common with any etiology of hypoperfusion. Hypotension, however, is most commonly secondary to hypovolemia. Hypotension from disruption of intrinsic cardiac function (cardiogenic shock) is much less common. CHF, a distinct clinical entity from cardiogenic shock, frequently results in increased blood pressure.

Treatment of Hypovolemia

The circulatory, metabolic, and toxic effects of hypovolemic hypoperfusion are best treated by rapid restoration of intravascular volume, thereby increasing MCFP, venous return, and oxygen delivery. In experimental studies, MCFP is not a clinically relevant measure since it is measured when the circulation is stopped (14). However, a recent study suggests that MCFP can be assessed in patients with an intact circulation by using an inspiratory pause from the ventilator (90).

Table 3.28 Cardiovascular Effects of Hemorrhagic Shock

Decreased venous return
Increased systemic vascular resistance
Decreased ventricular contractility
Decreased ventricular compliance
Increased atrial contractility
Transcapillary refill of water to restore plasma volume
Intravascular protein replenishment from preformed extravascular protein

Source: From Ref. 3.

Table 3.29 Cellular Effects of Hemorrhagic Shock

Diminished transmembrane potential difference
Increased intracellular sodium
Decreased intracellular ATP

A more specific approach to monitoring the effect of intravascular volume augmentation is repeated measures of cardiac output, the generation of a "Starling Curve" for each patient. While a well accepted demonstration of Starling's Law of the Heart is a subject of controversy, documenting an increase in cardiac output with augmented vascular volume substantiates the diagnosis of hypovolemic hypoperfusion for that individual (91–93).

In general, two types of fluid, crystalloid and colloid (Table 3.30), have been used for volume replacement and augmentation. Red cells are very effective when needed. After hemorrhage is arrested, administration of red cells results in increased cardiac output, increased oxygen carrying capacity, as well as slight, if any, leakage of red cells into the interstitium even in case of increased capillary permeability. Potential advantages and disadvantages of resuscitation fluids are provided in Tables 3.31 and 3.32.

Fresh frozen plasma (FFP) should not be used primarily as a colloid. It should be used only when hypovolemia is accompanied by bleeding and a deficiency in intrinsic or extrinsic coagulation proteins. Such a deficit is likely following trauma and the early use of FFP when massive RBC transfusion is provided has been shown to decrease morbidity and mortality (94). In general, RBCs are used to replace lost red cells and administered until the serum hemoglobin approaches 7–8 gm/dL. When restoration of cardiac output is difficult or does not appear adequate to meet oxygen demand, increasing hemoglobin to 10 gm/dL may be indicated. This is most likely to be useful in patients with a cardiogenic etiology of hypoperfusion rather than simple hypovolemia. However, documentation supporting that oxygen consumption will increase with such an elevation in hemoglobin is sparse (7,95).

Much more controversial than the appropriate use of FFP and RBCs is the advantages and disadvantages of the various crystalloid and colloid solutions previously listed. In general, most investigators agree that colloid administration results in less sodium and less water administration as compared to isotonic crystalloid solutions. In addition, plasma oncotic pressure is higher

Table 3.30 Fluids for Hypovolemia Resuscitation

1. Crystalloid
• Isotonic
Ringer's lactate
0.9% saline
• Hypertonic saline
2. Colloid
• Red blood cells
• Fresh frozen plasma
• Albumin
• Processed human protein
• Low molecular weight dextran
• Hydroxyethyl starch

Table 3.31 Crystalloid Solutions

1. Isotonic solution advantages
Inexpensive
Readily available
Replenishes ECF
Freely mobile across capillaries
No increase in lung water
2. Isotonic solution disadvantages
Rapid equilibration with interstitial fluid
Lowers serum oncotic pressure
No oxygen carrying capacity
Increase in systemically perfused interstitial fluid

Abbreviations: ECF = extracellular fluid.

following colloids. Still debated is whether the increased total body sodium and water gain from crystalloid is detrimental to organ function following resuscitation of the circulation. Summative evaluation of the crystalloid–colloid comparison favors neither (96–99).

Since hypoperfusion begets inflammation, especially in the context of ischemia/reperfusion, intense investigation has focused on the potential for various crystalloid and/or colloid formulae to diminish hypoperfusion-associated systemic inflammation (Table 3.33). At present, the L-dimer lactated Ringer's solution is the most practical selection (99,100).

When a hypovolemic patient is receiving large volumes of crystalloid or colloid and not responding well to therapy (most often seen in severe septic shock), dopamine administration is a logical adjunct since dopamine increases left ventricular filling pressures as it increases cardiac output. This may occur at the expense of increasing myocardial oxygen demands. Once adequate vascular volume is attained, usually the dopamine can be discontinued.

Pericardial Tamponade

The primary mechanism for decreased venous return with pericardial tamponade is an extracavitary increase in CVP. The etiologies of tamponade in surgery are most commonly chest trauma (penetrating and blunt) and bleeding after cardiac surgery. Physical examination classically reveals evidence of hypoperfusion along with distended neck veins, muffled heart sounds, and an increased paradoxical pulse (>15 mm Hg). The EKG may show low voltage, the CVP will often be elevated, and a chest X-ray may show an enlarged heart. With severe hypovolemia, the CVP may be normal despite tamponade and become elevated only after fluid resuscitation.

It is important to distinguish this etiology of hypoperfusion from CHF or cardiogenic shock since reducing fluid intake and administering a diuretic would reduce venous return further in tamponade. As stated, CHF usually results in a normal or elevated blood pressure.

Table 3.32 Colloid Solutions (Other Than Red Cells)

A. Advantages
   1. Less water administered (more resuscitation per cc)
   2. Less sodium administered
   3. Less decrease in oncotic pressure
   4. Acid buffer (fresh frozen plasma)
B. Disadvantages
   1. Expensive (albumin, Plasmanate, fresh frozen plasma)
   2. Adverse reactions (hypotension with Plasmanate)
   3. Transmissible disease (fresh frozen plasma)
   4. Increased interstitial oncotic pressure
   5. Depressed myocardial function (albumin)
   6. Depressed immunologic function (albumin)
   7. Delayed resolution of interstitial edema
   8. Coagulopathy (low molecular weight dextran)
   9. Acute lung injury (fresh frozen plasma)

Table 3.33 Fluid Administration and Resuscitation Inflammation

Fluid	Advantage	Disadvantage
Lactated ringer's D-isomer lactate	Inexpensive	Augments systemic inflammation
Lactated ringer's L-isomer lactate	Decreased inflammation	No specific clinical trials
Hypertonic saline	Less inflammation	Hypernatremia, hyperchloremia
HS-dextran	Less inflammation	No survival advantage in humans
Ethyl pyruvate	Less inflammation	
Hetastarch	Less volume	Augments systemic inflammation

Severe tamponade results in hypotension. Therefore, tamponade simulates cardiogenic shock more than CHF. Since cardiogenic shock requires a major insult to myocardial function, hypotension with an elevated CVP should increase suspicion of tamponade or a tension pneumothorax unless rather obvious evidence of severe myocardial malfunction is obtained.

While removal of the fluid surrounding the heart (pericardiocentesis) is the most effective therapy, venous return will also improve by increasing MCFP with intravenous fluid.

Tension Pneumothorax

Tension pneumothorax reduces venous return by producing an extracavitary increase in CVP and by increasing the RV in the chest. Tension pneumothorax may occur spontaneously from rupture of a bleb, or more commonly following penetrating or blunt trauma. Physical examination reveals evidence of decreased perfusion along with tympany and decreased breath sounds over the affected thorax, tracheal deviation away from the affected thorax, and distended neck veins.

Treatment consists of emergently releasing the tension (e.g., placing a 14-gauge needle into the chest, placing a finger in a large penetrating injury), followed by closed thoracostomy. Again, administration of intravenous fluid to raise MCFP is also beneficial, and neck vein distention may not be evident with severe hypovolemia.

Increased Abdominal Pressure

Increased abdominal pressure (>20 mm Hg) diminishes venous return by increasing intrathoracic pressure, producing an extracavitary increase in CVP, and increasing RV in abdominal veins. Increased abdominal pressure may be particularly detrimental to renal blood flow.

Abdominal pressure may be increased by various mechanisms (Table 3.6) and is most easily measured by using a bladder catheter (see chap. 5).

Physical examination will most often reveal evidence of hypoperfusion along with a tensely distended abdomen and possibly distended neck veins. The most effective treatment is to provide relief of the pressure. However, aggressive fluid management to increase MCFP may be the only option selected in some cases where, for instance, exploration of the abdomen is considered prohibitively risky. When hemodynamics and respiratory function (i.e., high peak inspiratory pressures required on the ventilator) are severely impaired by increased abdominal pressure, then opening the abdomen and using a temporary covering system is recommended (chap. 5).

PEEP (see chap. 6)

PEEP also diminishes venous return by increasing CVP from an extracavitary force and increasing RV in the thorax. While several other mechanisms have been argued for decreased cardiac output with PEEP, the primary mechanism is decreased venous return. Similar to increased abdominal pressure, if PEEP cannot be diminished, then the primary therapy is to administer fluids to increase MCFP.

Cardiogenic Hypoperfusion

Congestive Heart Failure

CHF is a common condition that most frequently occurs secondary to the etiologies mentioned in Table 3.34. Although difficulties with both contraction (systolic function) and relaxation (diastolic function) may coexist, an estimated 40% of patients have normal systolic function at the time of CHF. Therefore, the concept of diastolic dysfunction has gained prevalence and has implications related to therapy (101–103).

Note that excessive administration of intravenous fluid is not included in this list of etiologies. Patients without heart disease will sequester little intravenous fluid unless other pathophysiological conditions are present (e.g., severe inflammation). During severe inflammation, fluid sequestration and weight gain are not indicative of an excess in intravascular volume. In fact, intravascular volume may be decreased despite a marked increase in total body salt and water (see chap. 4). Only patients with new or underlying heart disease or

Table 3.34 Common Etiologies of Congestive Heart Failure

Systolic Failure (loss of myocytes, failure to contract)
• Acute ischemia
• Acute cardiomyopathy
Diastolic Failure (hypertrophy of myocytes, failure to relax)
• Hypertension
• Valvular heart disease
• Restrictive cardiomyopathy
• Mitral stenosis
• Constrictive pericarditis
• Post infarction hypertrophy

unrelenting anuric renal failure will develop CHF secondary to intravenous fluid therapy. In other words, the disease is in the patient, not in the fluid.

Ventricular physiology concepts are more relevant than venous return physiology for the understanding and management of CHF. Classically, CHF is described as a fall in cardiac output secondary to overstretching one or both ventricles (markedly increased preload) and decompensation of the Starling mechanism. As mentioned, decreased ventricular compliance and decreased filling with hypertrophy rather than overstretching may be responsible for the clinical physiology of CHF (salt and water sequestration, elevated ventricular filling pressures, increased extravascular lung water) without overstretching. In addition, other cardiac diseases (i.e., mitral stenosis, mitral regurgitation, left atrial myxoma) may produce a clinical picture similar to ventricular failure but with normal or increased ventricular function.

Regardless of the etiology, most often, the clinical presentation of CHF is secondary to increased pulmonary hydrostatic pressure along with decreased ventricular outflow via the aorta. The increase in hydrostatic pressure results in increased lung water and symptoms of respiratory distress, along with mild-to-moderate hypoxia (see chap. 6). Usually, CHF results in a mild-to-moderate reduction in cardiac output, which will decrease oxygen delivery, decrease arterial filling, and stimulate the sympathetic nervous system that results in tachycardia and vasoconstriction, mechanisms that maintain or, more frequently, elevate mean arterial pressure. Decreased cardiac output also results in vasopressin release as well as renal hypoperfusion, stimulation of renin, angiotensin production, and subsequent aldosterone secretion (104,105).

The neurohumoral responses to decreased cardiac output serve to further increase preload (renal conservation of sodium and water) and increase afterload (elevated mean arterial pressure), both of which may aggravate poor ventricular function and/or pulmonary water accumulation.

Natriuretic peptides (atrial and brain) are hormones that augment renal sodium and water excretion and the atrial peptide increases with atrial distention. The blood concentrations of both hormones are increased in CHF, and there appears to be renal resistance to the diuresis effect (104,105).

Physical Examination

The clinician must remember that this disease is called CHF. Physical examination should be directed at assessing *HEART* function. Most often, clinicians infer the status of cardiac function on the basis of lung status, amount of peripheral edema, calculated fluid balance, or the response to diuretics. The physical examination parameters that assess cardiac function are listed in Table 3.35. Of these, the S3 gallop is the most specific, but unfortunately not the most sensitive, evidence for ventricular failure (17). As stated above, blood pressure is well maintained or elevated (105). In fact, hypotension on a cardiac basis is delegated to a distinct clinical entity—cardiogenic shock. Therefore, a hypotensive patient either has cardiogenic shock or a more common cause of hypotension (e.g., hypovolemia, vasodilation).

Clinical evidence of increased lung water (tachypnea, rales, bronchospasm) may be present with any etiology of pulmonary edema (cardiogenic and noncardiogenic) or may

Table 3.35 Physical Examination Assessment of Heart Function

Heart rate
Rhythm
Blood pressure
JVP
S3 gallop
Murmurs

Abbreviations: JVP = jugular venous pressure.

Table 3.36 Congestive Heart Failure Laboratory DX

Chest X-ray—non-specific
Natriuretic concentrations
Measured CVP, PAOP, LAP
Cardiac catheterization
Echocardiogram

be simulated by other disease, such as atelectasis, pneumonia, COPD, or asthma. Diagnostic and therapeutic decision-making based primarily on lung status can be misleading and dangerous (see chap. 6).

Laboratory Aids

Laboratory aids in the diagnosis of CHF are listed in Table 3.36. The chest X-ray may be misleading as an assessment of both the amount of water accumulated in the lungs and etiology of water accumulation (see chap. 6). With normal lungs subjected to increased hydrostatic pressure, a relatively predictable sequence of radiographic changes is noted (22):

Hydrostatic Pressure (mm Hg)	X-Ray
<15–18	Normal
18–22	Cephalization
20–27	Perihilar haze
25–30	Rosettes
>30	Dense alveolar infiltrates

If a particular hydrostatic pressure is present for more than 24 hours, the chest X-ray should show corresponding changes. If not, another etiology of the chest X-ray findings should be considered.

Measurement of B-type natriuretic peptide (BNP) and N-terminal pro-BNP blood concentrations has been advocated for the diagnosis of CHF in the emergency department setting. However, these blood levels can be increased in patients with systemic inflammation from mild to severe (107,108). Therefore, this measurement will not provide sufficient diagnostic specificity for most patients with surgical critical illness.

CVP measurement is discussed in detail in the section on "Cardiovascular Physiology." Most often, patients with normal hearts and patients with chronic ventricular malfunction will exhibit a CVP that is within a few mm Hg of PAOP, making CVP measurement a useful laboratory test for CHF. When acute or chronic disease is present, which would be expected to produce significant discrepancy between the left and right ventricular or atrial function (acute MI, mitral stenosis, mitral regurgitation), CVP may be unreliable.

PAOP, not pulmonary artery diastolic pressure, is a reliable measure of LAP. Since pulmonary vascular resistance is increased by many diseases, PAOP may be low or normal despite increased mean and diastolic pulmonary artery pressure. In fact, when a pulmonary artery catheter does not provide a good occlusion pressure tracing, an elevated pulmonary artery diastolic

Table 3.37 Treatment of Congestive Heart Failure

1. Reversal of underlying disease
   A. Rx hypertension
   B. Coronary artery bypass
   C. Valve replacement
   D. Rx myopathy
2. Reduce preload
   A. Decrease water intake
   B. Diuretics
   C. Venous dilation
      i. Nitroglycerin
      ii. Calcium channel blockers
      iii. Narcotics
3. Reduce afterload
   A. Nitroprusside
   B. Antihypertensives
   C. Diuretics
   D. Narcotics
4. Increase contractility
   A. Intravenous inotrope—dobutamine, milrinone
5. Increase arterial oxygen
   A. Supplemental O_2
   B. Mechanical ventilation

pressure with a normal CVP should not be presumed to be secondary to increased LAP. Instead, a potential etiology of increased pulmonary vascular resistance should be sought.

The PA catheter measurements of an elevated (>18 mm Hg) right and/or LAP with a low cardiac index, but without hypotension, is the most specific, readily available continuous method to make a diagnosis of CHF in the critical care setting (22). Echocardiograms and cardiac catheterization are not commonly used to make the diagnosis of CHF, but rather to determine an etiology.

Treatment

Similar to the misapplication of lung-related information to make a diagnosis of CHF, using the lung as the primary measure of therapy is also misdirected. Once arterial oxygen saturation is 90% or greater (usually at a PaO_2 of ≥60 mm Hg), little benefit in oxygen delivery is realized by further therapy directed at the lungs. The primary goal in treating CHF is to improve heart function, cardiac output, and, thereby, oxygen delivery. Commonly employed treatment options for CHF are listed in Table 3.37. Using this logic, diuretics are not employed primarily to treat pulmonary edema, but to reduce preload in the overstretched heart and improve cardiac output. Since hemodynamics is the focus of treatment, hemodynamic variables (pulse, blood pressure, appearance or disappearance of an S3, skin color, and temperature) as well as mental status and spontaneous urine output are more valuable determinants of cardiac response to therapy than the physical examination of the lungs, chest X-ray, and arterial PO_2.

If reducing preload with a diuretic does not improve perfusion, then the common occurrence of well maintained or elevated mean arterial pressure makes arterial and venous dilation (reduced afterload and preload) the next logical step. Since increased wall tension and afterload will increase myocardial oxygen consumption, an increase in cardiac output from diuresis and vasodilation should not increase, and might decrease, myocardial oxygen demand.

If the above therapies prove insufficient, then inotropic therapy may be employed, but usually these agents are initiated for cardiogenic shock, not CHF (106,109). When inotropic drugs are administered, cardiac output monitoring (PAC, EDM, TPD) is especially useful to measure the response to drug manipulation. The end points of therapy include the following:

(1) good clinical perfusion status (normal blood pressure, pulse, mental status, temperature and color of extremities, spontaneous urine output); (2) good cardiac index (>2.5 L/min/M^2); (3) no metabolic acidosis; (4) normal lactic acid level; (5) normal mixed venous PO_2 and/or saturation (30–35 mm Hg and 65–70%, respectively).

The inotropic agents of choice for CHF are dobutamine and milrinone both of which increase cardiac output while decreasing left ventricular filling pressures and decreasing afterload (106). Dopamine is not as useful since filling pressure tend to increase as cardiac output improves. Importantly, dopamine may exert this effect even in the renal dose range.

Cardiogenic Shock

Cardiogenic shock, or hypotension on a cardiac basis, requires severe disruption of cardiac function (cardiac index <2.2 L/M^2) from etiologies such as those listed in Table 3.38. Acute myocardial infarction is the principle mechanism. Hypoperfusion of this magnitude is associated with high mortality (22,109).

In general, the diseases listed in Table 3.38 are not subtle and do not gradually accrue alterations in cardiac function that result in severe hypoperfusion and hypotension. As mentioned previously, hypotension is more often a consequence of hypovolemia and/or vasodilation than the result of severe impairment of cardiac function. When a clinician makes a decision not to administer fluid to a hypotensive patient, that clinician is actually making a de facto diagnosis of cardiogenic shock for that patient. Cardiogenic shock is the only hypotension-associated circulatory deficit that can be worsened by the administration of fluid. Since cardiogenic shock is secondary to severe, usually obvious cardiac disease, the clinician should be able to readily document the sudden occurrence of such a major insult to cardiac function (EKG changes, elevated troponin). In addition, cardiogenic shock demands the highest level of critical care monitoring and potential for intervention that a hospital can provide. Therefore, if the clinician at the bedside considers hypotension to be cardiac in origin, he/she should then proceed to document the etiology and engage critical cardiac services. If the clinician does not provide such documentation and engagement, then he/she should consider the patient to be in a state of hypovolemic hypoperfusion, not cardiogenic shock.

Physical Examination

Physical examination will reveal hypotension, tachycardia, tachypnea, peripheral vasoconstriction, distended neck veins, agitation, and confusion. Traditionally, hypotension is designated as a systolic pressure <90 mm Hg. However, a decrease >30 mm Hg below the patient's basal is also considered sufficient hypotension (109). An S3 gallop may be apparent, and when valvular dysfunction is present, associated murmurs may be auscultated.

Table 3.38 Etiologies of Cardiogenic Shock

1. Acute ischemia
   A. Ventricular wall infarct
   B. Papillary muscle infarct
   C. VSD rupture
2. Acute valvular disease mitral, tricuspid, aortic regurgitation
3. Arrhythmias
   A. Rapid supraventricular
   B. Bradycardia
   C. Ventricular tachycardia
4. Miscellaneous
   A. End-stage cardiomyopathy
   B. Severe myocardial contusion
   C. Severe myocarditis
   D. Severe LV outflow obstruction
   E. Severe LV inflow obstruction

Laboratory Aids

Cardiogenic shock is associated with chest X-ray evidence of pulmonary edema, metabolic acidosis (lactic acidosis), increased blood urea nitrogen (BUN) and creatinine, elevated CVP, PAOP, and decreased cardiac index (<2.2 l/min./m^2). Frequently, a cardiogram will reveal evidence of acute ischemia or infarct and/or arrhythmias. An echocardiogram can provide information about ventricular wall motion and valve function.

Treatment

As always, treatment is based on the etiology. Arrhythmias are generally the most readily treated etiology of severe cardiac impairment. Arrhythmias are diagnosed and treated as described in *Advanced Cardiac Life Support* documents as well as other texts.

When the etiology is not an arrhythmia, the same sequence of interventions used to increase cardiac output in CHF may be used for cardiogenic shock. However, hypotension (often <90 mm Hg systolic) makes use of vasodilators alone less attractive. Therefore, a combination of inotropic support and vasodilation is frequently employed. Mechanical support of the heart using the intra-aortic balloon pump (IABP) increases cardiac output while reducing preload and afterload (Fig. 3.11) (110). IABP may be more successful than high-dose dobutamine in supporting patients at the time of severe cardiac impairment. IABP use may be adequate to support a patient until cardiac function improves or may be required until a surgical solution (e.g., replacement of the aortic valve or coronary revascularization) can be accomplished.

The complications of IABP use are listed in Table 3.39; the most frequent is lower extremity ischemia, usually on the side where the balloon pump was inserted.

Postoperative Open Heart Hypoperfusion

Postoperative open heart patients may suffer decreased cardiac output secondary to the mechanisms listed in Table 3.40. Fortunately, these patients are usually well monitored and

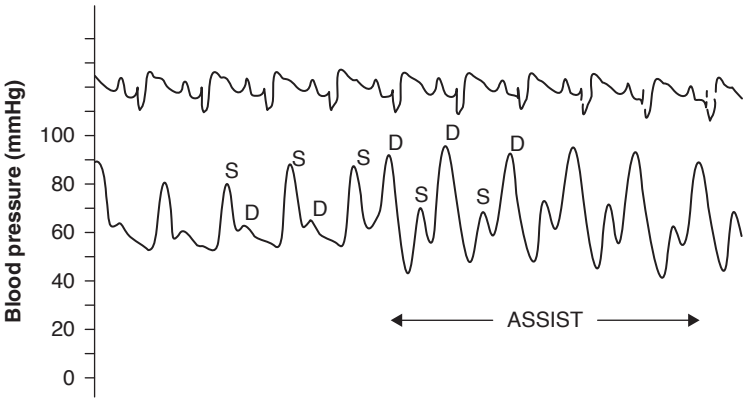

Figure 3.11 The effects of intra-aortic balloon pumping on systolic and diastolic pressure. Systolic pressure is reduced, decreasing left ventricular afterload. Diastolic pressure is increased, which increases coronary perfusion pressure. However, ventricular end-diastolic pressure is reduced, indicating a reduction in preload.

Table 3.39 Complications of Intra-Aortic Balloon Pumps

- Lower extremity ischemia
- Thrombocytopenia
- Infection
- Aortic dissection
- Free perforation

Table 3.40 Postoperative Open Heart Hypoperfusion

- Hypovolemia
- Tamponade
- Increased afterload
  - –Drugs
  - –Hypothermia
  - –Hypovolemia
- Congestive heart failure
- Cardiogenic shock
- Severe inflammation
  - –Postpump syndrome
  - –Pancreatitis
  - –Ischemic intestine

careful evaluation of hemodynamic variables will allow for logical therapy. The combination of hypovolemia and hypothermia can result in hypertension despite a low cardiac output. In addition, decreased left ventricular compliance from increased afterload (hypertension) may result in a normal or elevated LAP or PAOP, suggesting a normo or hypervolemic state.

Keeping these concepts in mind, the management of postoperative cardiopulmonary bypass patients will generally be the same as described in previous sections. However, unique to this patient population is the risk of tamponade from mediastinal bleeding that is too rapid to be evacuated by the mediastinal chest tubes or has clotted off the chest tubes. Tamponade must be considered whenever increasing atrial pressures are associated with decreasing cardiac output. Since hypovolemia aggravates the fall in cardiac output with tamponade, incorrectly diagnosing CHF or cardiogenic shock followed by a therapeutic decreased fluid administration and/or diuretics can be gravely detrimental. Fortunately, tamponade is usually preceded by increased mediastinal chest tube drainage and fluid resuscitation is underway when tamponade becomes more apparent. When properly diagnosed, tamponade usually requires rapid return to the operating room to control hemorrhage.

More difficult to manage is the occasional patient who develops evidence of severe systemic inflammation following cardiopulmonary bypass. These patients with underlying heart disease may manifest a wide spectrum of cardiac alterations related to severe inflammation. The etiology and management schemes for inflammation-induced cardiac malfunction are discussed in the Inflammation chapter. Once again, the astute clinician must be alert to the possibility that an impaired circulation may be secondary to severe inflammation.

Postoperative Major Vascular Surgery Hypoperfusion

Common etiologies of postoperative major vascular surgery hypoperfusion are listed in Table 3.41. The manifestations of total body hypoperfusion, etiologies, and management are similar to those described above. The recognition of regional hypoperfusion may be simple (obvious lower extremity ischemia) or difficult (diagnosis of intestinal ischemia). Particularly life threatening is large and small bowel ischemia and/or infarction. Clinical clues suggesting this condition are listed in Table 3.42.

Physicians who regularly attend these patients may recognize the subtleties of postoperative fluid requirements and abdominal findings. For those with less experience, patients usually do not have a bowel movement during the first 24 hours after major abdominal surgery, and such an event, especially accompanied with blood, should lead to further study. With regional ischemia, lactic acidosis will be persistent despite evidence of good total body oxygen delivery. The large bowel can be viewed by sigmoidoscopy or colonoscopy, looking for evidence of mild or partial ischemia versus confluent or severe injury. Evaluation of the small bowel is more difficult and can require abdominal explorationfor proper assessment. Ischemic and especially infarcted intestine are typically more life threatening than further surgery per se.

Table 3.41 Postoperative Major Vascular Surgery Hypoperfusion

I. Total Body
• Hypovolemia
• Hypothermia
• Hypertension
• Congestive heart failure
• Cardiogenic shock
II. Regional
• Extremity(ies)
• Large intestine
• Small intestine
• Brain
• Kidney(s)

Table 3.42 Intestinal Ischemia Diagnosis

• Blood or melena per rectum
• Diarrhea
• Large fluid sequestration
• Abdominal tenderness
• Leukocytosis
• Lactic acidosis

Table 3.43 Cardiac Trauma

• Blunt cardiac injury
• Cardiac tamponade
• Blunt chamber rupture
• Penetrating wound
• Valvular disruption
• Tension pneumopericardium

Cardiac Trauma

Cardiac trauma may also result in hypoperfusion secondary to the etiologies listed in Table 3.43 and present with a clinical picture that can range from no hemodynamic insult to sudden death. Since obtaining a myocardial biopsy is impractical, the specific diagnosis of blunt cardiac injury without a major disruption of heart anatomy is difficult to ascertain. Instead, markers for potential myocardial injury (EKG changes, elevated troponin levels, echocardiogram) provide sufficient diagnostic information for likely myocardial insult, be it anatomically or physiologically based (111,112).

In essence, the most severely injured patients are at the highest risk for cardiac alterations and are likely to be observed in a critical care environment where such abnormalities (e.g., arrhythmias, conduction disturbance, CHF, cardiogenic shock) will be recognized and managed as with any other patient.

Usually, cardiac tamponade is secondary to blunt or penetrating chamber injury that will require operative repair. Chamber injury may also result in exsanguination if open to the pleural space. Acute valvular insufficiency may result in CHF or, more likely, cardiogenic shock and may require valve replacement. Tension pneumopericardium, usually associated with pneumothorax, may respond to chest tube placement on the affected pleural space or require more direct therapy (pericardial needle or chest tube insertion).

END POINTS FOR RESUSCITATION

As stated at the outset of this chapter, the circulation provides oxygen for cellular oxidative phosphorylation and removes carbon dioxide and other metabolites to allow excretion. The principal features of an adequate circulation are organ and cellular manifestations of sufficient

cell energetics to meet metabolic demands. Many of the preceding sections detail the clinical and laboratory information that indicate sufficient or insufficient oxygen delivery and cell metabolic state. This section summarizes those parameters (113):

I. Bedside hemodynamic measurements are insufficiently sensitive to identify all cells and tissues at risk.
II. Disease-induced hypothermia is a marker of metabolic deficit.
    a. Active warming improves outcome (induced hypothermia may have a role in isolated head trauma)
III. Metabolic markers augment identification of cells at risk.
    a. Increased lactic acid
    b. Decreased ionized calcium
    c. Increased glucose in a non-diabetic
    d. Hypokalemia in a trauma patient
    e. Increased tissue pCO_2 concentration
    f. Decreased tissue pO_2 concentration
IV. Restoration of the circulation includes documentation of adequate oxygen delivery.
    a. Central venous saturation >70%
    b. Mixed venous saturation >65%
    c. Oxygen delivery—at least 500 $cm^3/min/m^2$
    d. Oxygen consumption—at least 145 $cm^3/min/m^2$
V. Rapid resolution of metabolic derangements is associated with improved outcome.
    a. Continue to monitor lactic acid until normal
    b. Continue to monitor tissue pCO_2 until normal
VI. Rapid restoration of oxygen delivery is associated with improved outcome.
    a. Continue to monitor venous oxygen saturation until normal
    b. Continue to monitor tissue oxygen concentration until normal
VII. Metabolic deficits can persist even after oxygen delivery is augmented.
    a. Definitions of the Ebb (poor oxygen consumption) and Flow (increased oxygen consumption) phases of shock
    b. Consider altering systemic inflammation in the Flow Phase (see chap. 4).
VIII. Resuscitation is completely achieved when all clinical and laboratory data indicate normal or augmented cellular energetics (resolution of the rude unhinging of the machinery of life).

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4 | Inflammation

LOCAL PROCESS

Inflammation presumably evolved as a process to achieve two principle benefits—wound healing and defense against microbiologic invasion. When insults are relatively small (i.e., elective groin hernia wound, facial acne), then the physiology and cellular functions of these two processes can be considered local, somewhat distinct, with little effect on the rest of the body (little systemic effect). But when insults are large (i.e., bilateral femur fractures with bilateral pulmonary contusions, perforated sigmoid diverticulitis), then the similarities between wound healing and host-defense mechanism become more apparent and associated with more evidence of systemic alterations.

First, here are descriptions of the more local physiology and cellular functions of wound healing and host defense, followed by descriptions of how wounds and microbiologic invasion result in systemic inflammation.

Wound Healing

When a wound is in the skin and subcutaneous tissue (the most common wound studied), the epidermal barrier is broken and keratinocytes release pre-stored interleukin-1 (IL-1). The subsequent response is bleeding and coagulation. Platelet activation results in the release of important chemoattractants [i.e., epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β)].

Damaged blood vessels initially constrict, but this is soon followed by vasodilation and increased capillary permeability secondary to the action of agents such as prostaglandin E2, prostacyclin, histamine, serotonin, and kinin. This vascular response results in the accumulation of protein-rich edema fluid (exudate). Leukocyte cells adhere to the damaged and leaky vessels.

Attracted by chemoattractants such as PDGF and IL-1, polymorphonuclear cells (PMNs) are the first leukocytes to migrate to the inflammatory site (within minutes if the circulation is good). PMNs serve to phagocytize dead tissue and foreign objects. Removal of bacteria may be assisted by opsonins and preformed antibodies. PMNs produce proteases and intracellular oxygen radicals that are critical for beneficial PMN activity. Besides proteases and oxygen radicals, PMNs can release IL-1. IL-8 is a potent PMN attractant produced by many cell types after incubation with IL-1 and tumor necrosis factor (TNF). The PMNs last only for hours.

Lymphocytes are the next cell to migrate into the wound. The role of the lymphocyte is less well understood, but depletion of T cells results in impaired wound healing.

Subsequently (within hours), tissue macrophages and circulating monocytes are attracted by substances such as PDGF, TGF-β, and IL-1, migrate into the injured area, and last for days to weeks. Wounds can heal without PMNs but not without macrophages that regulate most of the continuing stages of inflammation and wound healing through mediators such as IL-1, PDGF, TGF-β, TGF-α, and fibroblast growth factor (FGF).

Fibroblasts migration and angiogenesis begin next. Fibroblasts are influenced by IL-1, PDGF, TGF-β, and TGF-α; angiogenesis is influenced by TGF-β, TGF-α, and EGF. The combined process of fibroblast proliferation and capillary budding produces a wound that is granular in appearance (granulation tissue), very vascular, and quite friable. Certain fibroblasts—myofibroblasts—have smooth muscle contractile elements that contract and diminish the area of a wound. In general, wound contraction continues until the lining cells from each edge of a wound meet (epithelialization for the skin). Therefore, slight contraction will follow wounds that are closed primarily, that is, with the lining edges apposed. Much contraction may occur in secondary healing, especially when wound edges remain widely separated for days to weeks.

Fibroblasts make collagen, usually accelerating at five days after tissue damage. Before this, fibrin is the principle wound substance besides sutures that holds a wound together. Collagen synthesis is also influenced by IL-1, PDGF, TGF-β, and EGF. Since the macrophage is an important source of these factors, mechanisms that increase (glucan administration) and decrease (the combined effect of hypoxia and endotoxin) macrophage function may result in increased or decreased wound strength, respectively.

A summary of cellular activity in wound healing is provided in Tables 4.1 and 4.2 (1,2).

Local Host Defense

Local host-defense mechanisms have been principally studied as the response to microbiologic challenge. Both an *innate immune* capacity (defenses that lack immunologic memory) and an *acquired* capacity (defenses with immunologic memory) are components of local host defense (Tables 4.3 and 4.4).

The first mechanism of local innate host defense is surface barrier function, best understood as the effect of the intact skin. Penetration through a barrier results in further stimulation of the innate response.

The polymorphonuclear leukocyte (PMN, neutrophil) is the earliest cell component that responds to pathogen penetration. The steps related to PMN infiltration and action are listed in Table 4.3. PMNs serve to phagocytose organisms and/or debris, kill microorganisms, and release enzymes and reactive oxygen species to enhance control of damaging materials. Complement coating of organisms enhances phagocytosis (3–7).

PMN activation also results in the release of cytokines (IL-1, IL-6, TNF-α, IL-8, IL-12), toxic oxygen radicals, peroxides, nitric oxide (NO), and lipid mediators of inflammation such as prostaglandins and leukotrienes, as well as platelet activating factor (PAF) (5).

Table 4.1 Normal Wound Healing/Normal Inflammation

Events	Cells responsible
• Coagulation	• Platelets
• Early inflammation	• PMN (first few hours)
• Later inflammation	• Monocytes (days) macrophages
• Collagen and mucopolysaccharide	• Fibroblasts (maximum deposition 7–10 days)
• Capillary budding	• Endothelial cells (maximum 7–10 days)
• Wound contraction	• Myofibroblasts
• Collagen remodeling	• Fewer fibroblasts and capillaries

Table 4.2 Functions of Wound Healing Cells

Cells	Function
• Keratinocytes	• Release IL–1
• Platelets	• Coagulation, release EGF, PDGF, TGF-β, VEGF
• PMN	• Phagocytosis, especially microbes, release IL-1, IL-8
• Macrophage	• Phagocytosis, stimulate fibroblast migration and growth, stimulate endothelial cell migration and growth, release FGF, PDGF, IL-1, IL-6, TGF-β, TGF-α
• Fibroblast	• Collagen deposition, TGF-β wound contraction, TGF–β, PDGF wound remodeling, FGF, TGF-β
• Endothelial cells	• Capillary budding, VEGF

Abbreviations: IL-1, interleukin 1; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; IL-8, interleukin 8; FGF, fibroblast growth factor; IL-6, interleukin 6; TGF-α, transforming growth factor alpha.

Macrophage infiltration follows PMN activation and accomplishes many of the same microbe suppression activities. In addition, macrophages are responsive to pathogen-associated molecular structures (PAMP) that are shared by entire classes of pathogens, such as lipopolysaccharides on Gram-negative bacteria. Macrophage recognition of a PAMP triggers activation before proliferation at the site (8). The macrophage also serves as an antigen-presenting cell for stimulation of the acquired immune system. However, the dendritic cell, also responsive to PAMP, is a more potent antigen-presenting cell that migrates to local lymph nodes to engage T cells (7).

The principal PAMP receptors are called toll-like receptors, first described in drosophila, and now considered a primary mechanism for activation of nuclear factor-kappa B (NF-κB), an important step in the production of cytokines and co-stimulatory molecules (8–10).

Natural killer cells can recognize "non-self" cells by absence of the major histocompatibility complex (MHC) class I. Since MHC class I is present on nucleated cells, most are not subject to threat. However, infection can alter the expression of MHC class I on infected cells and result in killer cell destruction (7,11).

Table 4.3 Components of Local Host Defense: Innate Response

- I. Surface barrier
  - A. Epithelial cells
    - i. Skin
    - ii. Mucosa
  - B. Constituents
    - i. Mucus
    - ii. Normal flora
- II. PMNs
  - A. Margination
  - B. Rolling
  - C. Adhesion to endothelial cells
  - D. Transmigration
  - E. Phagocytosis
  - F. Release of toxic molecules
- III. Macrophages
  - A. Phagocytosis
  - B. Stimulation of angiogenesis
  - C. Stimulation of contraction
- IV. Dendritic cells—presentation of antigens
- V. Natural killer cells—augment removal of "non-self"
- VI. Complement activation
  - A. Opsonization
  - B. Stimulation of inflammatory cells
- VII. Systemic alterations in the "local" response
  - A. Fever
  - B. Acute phase reactants

Table 4.4 Components of Local Host Defense: The Acquired Response

- I. Antigen presentation
  - A. Dendritic cells
  - B. Macrophages
  - C. B cells
- II. T-cell activation
- III. T-cell differentiation
  - A. TH1—cellular immunity
  - B. TH2—humoral immunity

Complement is another component of the innate immune system that can be activated via three pathways (Figure 4.1). The classical pathway is activated by antibodies [immunoglobulin (IgG, IgM] binding to antigen and is part of acquired immunity. The mannan-binding lectin (MBL) pathway is activated by binding of MBL, an acute-phase reactant secreted by the liver, to bacteria or virus surface components. In the alternative pathway, the complement component C3 becomes "spontaneously activated" to C3b that then binds to the surface of a pathogen and promotes opsonization. Overall, activation of complement results in opsonization, recruitment of inflammatory cells, and direct killing of pathogens (5).

Small amounts of tissue injury and infection can presumably result in principally autocrine and/or paracrine effects that do not result in any cellular activity distant from the site of the stimulus. However, sufficient tissue injury and infection initiates an endocrine effect such

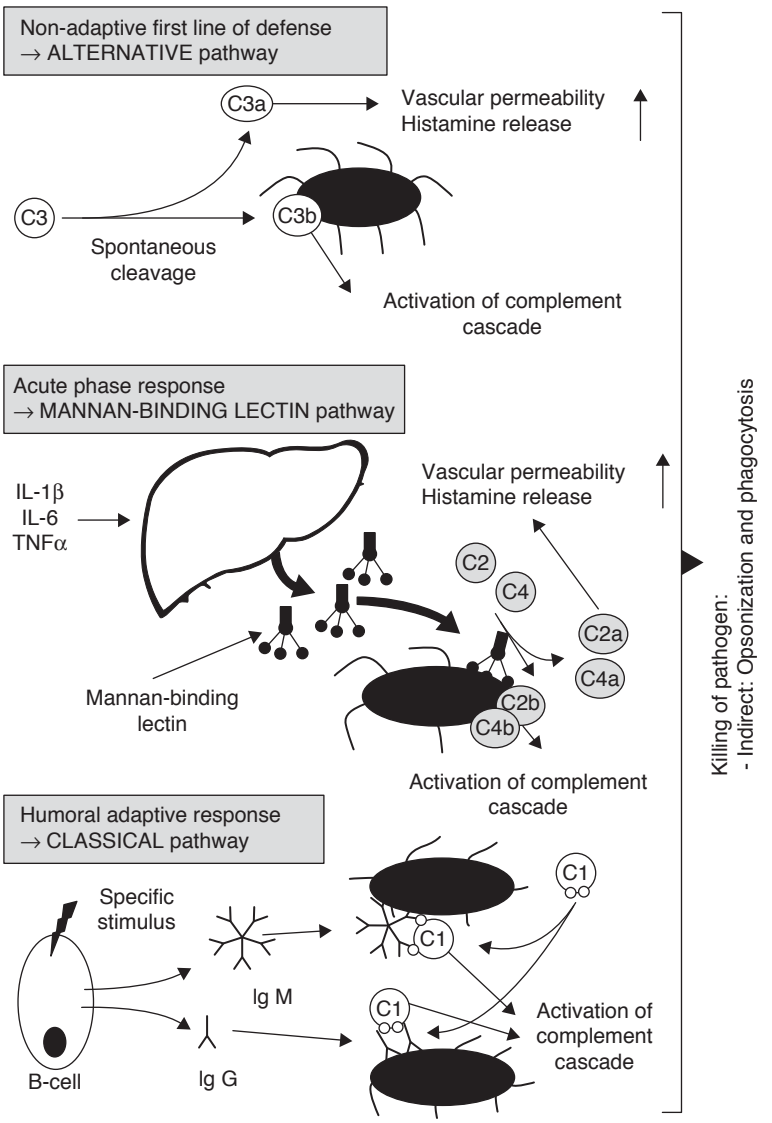

Figure 4.1 Complement activation at different time points following bacterial invasion. First is the alternative pathway that is triggered by binding of C3 to the surface of a pathogen. Second, the acute-phase response results in a mannan-binding lectin that can bind to bacteria and activate complement. Finally, the classic pathway can be triggered by specific antibody that has accrued against an organism. *Source*: From Ref. 5.

that mediators of inflammation cause systemic alterations that can be adaptive or maladaptive, usually depending on the magnitude of insult and, sometimes, the magnitude of the individual's response (see section on "Severe Systemic Inflammation").

Adaptive systemic effects that appear to enhance host defenses are fever (secondary to IL-1, IL-6, and TNF-α) and liver synthesis of acute phase reactants [i.e., C-reactive protein (CRP) and MBL], which are enhanced by these same cytokines (5).

As with wound healing, the local response to pathogen penetration can result in complete resolution of tissue injury with little scar formation. However, incomplete resolution can result in ongoing inflammation, granulation tissue formation, and fibrosis, collectively called an abscess. An abscess may or may not be associated with systemic alterations, again dependent on the magnitude of the threat as well as that of individual response.

Acquired immunity depends on the presentation of foreign antigens to T cells. Dendritic cells, macrophages, and B cells serve to present antigen to unstimulated T cells. Antigens that gain access to the circulation can be captured by antigen-presenting cells in the spleen and stimulate T cell activation at that site. The naïve T cells can then differentiate into Th1 cells that augment cell-mediated immunity or Th2 cells that augment humoral immunity. This differentiation is linked to a complex interaction of inflammatory mediators. Full activation of acquired immunity takes several days (5).

In addition to these inflammatory cell activities, a local site of infection is characterized by arteriolar vasodilation, increased blood flow, increased capillary permeability, exudation of plasma, and pain. This results in the complaint of pain (dolor), and the findings of erythema (rubor), edema (tumor), and warmth (calor).

Stimulants to Host-Defense Responses

Alarmins

The recognition that the inflammatory response to wounded tissue is similar to cell processes during infection has highlighted that host defense is not strictly limited to recognition of "self" from "non-self." Perhaps the most striking example of variability in recognition of "self" is the difference in inflammatory response to programmed cell death (apoptosis) and cell disruption by injury and/or ischemia (necrosis/oncosis). Apoptosis results in little inflammatory response, but necrosis incites a response as vigorous as wounding or infection. Unprogrammed cell death (necrosis) releases molecules (collectively termed "alarmins") that are not released during apoptosis, can be augmented by inflammatory cell activity, and can result in activation of receptor-sensitive cells that enhance acquired immunity. Molecules that have been catalogued as alarmins include the following: High Mobility Group Box 1 (HMGB1), a nuclear protein; heat-shock proteins (HSP); uric acid. Alarmins and PAMP have been combined under the term damage-associated molecular patterns (DAMP) to enhance the consideration that tissue injury and infection can cause similar host-defense responses (9).

Ischemia/Reperfusion

Oxidative stress is defined as a state of excess reactive oxygen intermediates (ROIs) compared with the endogenous antioxidants of the host. Oxidative stress can result from an excess of ROI production or a deficit in antioxidants. The production of ROI is one mechanism whereby phagocytes (PMNs and macrophages) kill invading organisms, an obvious benefit. However, while intracellular ROI can provide potent host-defense activity, extracellular ROI can cause injury to host tissues and also augment the local and systemic inflammatory response (12).

Phagocytic cell activation is not the only mechanism for excess ROI production. Ischemia results in depletion of cellular ATP and accumulation of xanthine and hypoxanthine as ATP is metabolized. Two intracellular enzymes [xanthine dehydrogenase (XD) and xanthine oxidase (XO)] can metabolize these breakdown products, with XD using NAD^+ as an electron acceptor, but XO using molecular oxygen. Cell energy deficits augment calcium influx into the cell that increases conversion of XD to XO. When oxygen is re-introduced (reperfusion), the action of XO results in the accumulation of superoxide anion and hydrogen peroxide, both toxic moieties to host cells (12–14).

Table 4.5 Oxidative Stress Molecules

I.	Superoxide (O_2^-•)
II.	Hydrogen peroxide (H_2O_2)
III.	Hydroxiy radical (HO)
IV.	Hypochlorous acid (HOCL)
V.	Peroxynitrate ($ONOO^-$)

While PMNs are required for the full expression of ischemia/reperfusion injury, endothelial cells appear to be particularly capable of ischemia/reperfusion ROI production, even in the absence of neutrophils. The ubiquitous presence of endothelial cells provides equally ubiquitous potential for nearby cell damage via oxidative stress mechanisms.

Molecules that participate in oxidative stress states are listed in Table 4.5. Additional mechanisms for ROI production include nitric oxide metabolism and lipid peroxidation as a feature of cell membrane damage. Interestingly, lipid peroxidation is also a principle mechanism of cell injury from ROI, illustrating the potential for repetitive ROI injury. Cell death from oxidative stress appears to be linked to excessive mitochondrial calcium accumulation (13).

Ischemia Alone (Hypoperfusion Begets Inflammation)

Insufficient oxygen delivery can cause activation of inflammatory cells and other innate host-defense mechanisms before reperfusion. Mountain sickness is associated with increased capillary permeability (lungs, brain) and elevated blood concentrations of IL-6 and CRP. Hypoxia has been shown to increase the activity of innate immune cells, and PMN activation has been documented during hemorrhage and during cardiopulmonary resuscitation. Finally, rapid restoration of the circulation (i.e., rapid improvement in delivery of oxygen to cells, before reperfusion mechanisms are activated) has been shown to diminish markers of inflammation (15–18).

SYSTEMIC PROCESS

While it is common for mild-to-moderate inflammatory conditions to result in some systemic manifestations (e.g., fever, tachycardia, leukocytosis, increased blood levels of CRP), more severe inflammatory conditions can cause life-threatening functional disturbances in organs distant from the principle inflammatory site, meeting the definition of severe systemic inflammation. In 1992, the concept of systemic inflammatory response syndrome (SIRS) was offered in keeping with the recognition that tissue injury with and without infection was capable of producing systemic alterations. The diagnostic criteria for SIRS are listed in Table 4.6 (19). While this listing included variables typically associated with severe, organ function-threatening systemic inflammation (i.e., hypothermia and leukopenia), the cataloguing of SIRS reflected severity only as related to infection (sepsis, severe sepsis, septic shock) and did not provide a more generic ranking of the severity of systemic inflammation per se. Since then, the magnitude of systemic inflammation-associated organ malfunction (MODS scores, SOFA scores) has been used to monitor severity and can, therefore, be used to identify severe systemic inflammation, regardless of etiology.

The magnitude of the systemic response to an inflammatory stimulus appears to be linked to two principle pathophysiologic mechanisms that cause cell function abnormalities: circulation deficits (too little oxygen delivery to cells); an excess of inflammatory toxins (cytokines, oxidative stress molecules, etc.). While each of these processes can be a primary manifestation of systemic inflammation, it is characteristic for both to be acting simultaneously to threaten cell function and/or viability.

Circulation Deficits (Inflammation Begets Hypoperfusion)

Mechanisms of inflammation-induced hypoperfusion are listed in Table 4.7. Vasodilation and increased vascular capacitance have been linked to activation of ATP-sensitive potassium channels

Table 4.6 Systemic Inflammatory Response Syndrome

I. Body temperature >38 C or <36 C
II. Heart rate greater than 90 BPM
III. Tachypnea, manifested by a respiratory rate >20 breaths per minute, or hyperventilation, as indicated by a $PaCO_2$ of <32 mm Hg
IV. An alteration in white blood cell count, such as a count >12,000/mm^3, a count <4,000/mm^3, or the presence of more than 10% immature neutrophils

Table 4.7 Mechanisms of Inflammation Induced Hypoperfusion

I. Increased capacitance (vasodilation), decreased MCFP, decreased venous return
A. Hyperpolarization of vascular smooth muscle membrane
B. Increased nitric oxide concentrations
C. Decreased vasopressin concentrations
II. Decreased vascular volume (exudation of plasma, decreased ECF—"third space" losses
A. Exudation at the site of tissue injury
B. Exudation at sites distant from site of injury
C. Fluid accumulation in the lumen of the GIT
D. Cell membrane deficits—migration of ECF into the intracellular space
III. Impairment of the microcirculation
A. Regional vasodilation/vasoconstriction
B. Plugging—leukocytes/platelets
IV. Myocardial depression
A. Ischemia—microcirculation
B. Myocardial depressant factors

Abbreviations: MCFP, mean circulatory flow pressure; ECF, extracellular fluid; GIT, gastrointestinal tract.

(from decreased intracellular ATP), the efflux of potassium from the cell, hyperpolarization of the cell membrane, and inhibition of calcium entry into the cell. Since augmented cytosolic calcium concentrations cause smooth muscle contraction, the inhibition of calcium entry limits vasoconstriction. Inflammatory stimuli increase the activity of inducible, calcium-independent, nitric oxide synthetase in endothelial and smooth muscle cells, resulting in vasodilation that is resistant to catecholamines and angiotensin II. In addition, a vasopressin deficiency (i.e., concentrations insufficient to produce arteriolar constriction) has been documented in prolonged hypotension following both hemorrhagic and inflammation-induced hypoperfusion (20–23).

Venous return is also threatened by a decrease in plasma volume from the migration of both plasma and interstitial fluid into sites collectively called "the third space." The exudation of plasma at the site of injury and/or infection is an obvious process of plasma volume depletion. But the other components of extracellular fluid sequestration (exudation at other sites, fluid accumulation in the gastrointestinal lumen, and enhanced intracellular water migration) are not so intuitive. Increased systemic capillary permeability is presumably secondary to the endocrine effects of inflammatory mediators on endothelial cells throughout the body, an effect most regularly witnessed during alterations in lung function, yet possible to identify in the glomerular capillary (24–27). Intestinal alterations are common with acute illness. The balance between secretion and absorption can be altered, resulting in further depletion of plasma volume (28). When inflammation is sufficiently severe, cell energetics and cell membrane function can be impaired, disturbing membrane pump function that maintains the normal concentrations of intracellular versus extracellular ions. Sodium pump deficits will result in increased intracellular sodium concentrations, causing migration of interstitial water into the intracellular space (29,30).

Systemic inflammation can result in marked alterations in the microcirculation, including constriction of larger arterioles, dilation of smaller arterioles, alterations in capillary flow, and plugging by leukocytes and platelets. These deficits may variously affect specific tissues. The intestinal tract appears to be particularly sensitive. Recently, the measurement of sublingual microvascular flow in human sepsis has demonstrated that the potential for marked reduction

in regional oxygen delivery is present even when global (i.e., cardiac output-based oxygen delivery) is excellent (31–33).

Myocardial depression is a common feature of severe systemic inflammation, even when the overall circulatory state is hyperdynamic (34). Systolic malfunction such as a global reduction in ejection fraction and/or regional wall motion abnormalities as well as diastolic dysfunction have been documented with echocardiography (35). Both cardiac troponin and NH_2 terminal pro-brain natriuretic peptide (NT-proBNP) elevations parallel the severity of depression as well as the prognosis (36–38). The mechanism(s) responsible for these alterations are imperfectly characterized, but include microcirculation ischemia and myocardial depressant factors that encompass a host of molecular mediators (34,35,39). Importantly, measurement of an elevated cardiac troponin or NT-proBNP does not necessarily "rule in" other cardiac diagnoses associated with these biomarkers, especially when severe systemic inflammation is present.

Excess Inflammatory Toxins

As mentioned in the Shock chapter, deficits in cell metabolism have been linked to toxic mechanisms that can inhibit cell function separately from oxygen metabolic pathways. The term cytopathic hypoxia has been applied to these metabolic alterations that mimic the changes from oxygen deficits (40,41). Severe systemic inflammation appears to be the principal clinical cause of cytopathic hypoxia. Several studies in humans have documented that decreased oxygen consumption and/or an inability to increase oxygen consumption following resuscitation are associated with high mortality (42–44). In essence, these patients exhibit continuing evidence of the Ebb Phase of shock despite efforts that improve total body oxygen delivery.

The concept of toxic cellular injury is supported by epidemiologic data showing higher concentrations of inflammatory biomarkers in the most severely ill patients (45–48). In addition, human studies have periodically demonstrated good tissue oxygen concentrations despite evidence of organ malfunction (49,50).

The molecular etiologies of cytopathic hypoxic have been associated with diminished delivery of pyruvate into the mitochondrial tricarboxylic acid cycle, inhibition of key mitochondrial enzymes, and activation of the enzyme poly(ADP-ribose) polymerase-1 (PARP-1) (40).

In addition to the potential for inflammatory toxins to cause metabolic alterations, the products associated with oxidative stress can cause direct cellular injury as described above (12). PMN activation is the primary mechanism for oxidative tissue injury and augmented PMN activation with tissue sequestration has been linked to multiorgan malfunction in both experimental and human investigations (51).

METABOLIC AND HORMONAL RESPONSE TO INFLAMMATION

The metabolic and hormonal response in severe tissue injury and systemic inflammation is linked to the Ebb and Flow phases of shock (Table 4.8) (52). As noted in the Shock chapter, persistence of the Ebb phase is usually lethal. Achievement of the Flow phase is associated with increased temperature, resting energy expenditure (REE), oxygen utilization, and glucose and fat oxidation. Amino acids are also used as substrate, and there is an increase in nitrogen loss. At three to four days following injury, the Flow phase can be at a maximum and then diminish gradually in association with resolution of ileus, spontaneous diuresis of "third space," and normothermia (53). When inflammation continues, most commonly secondary to new or unresolved infection, persistence of the Flow phase can be associated with progressive organ failure and death, sometimes despite the eradication of the principal inflammatory focus (53).

Carbohydrate

Glucose is commonly elevated in both the Ebb and Flow phases. In the Ebb phase, the glycolytic and glucogenic endocrine response is associated with a poor insulin secretion (54). During the Flow phase, the combination of increased epinephrine, cortisol, glucagon, lactate, and release of glucogenic amino acids from muscle (especially alanine) results in elevated glucose, often despite increased blood insulin concentrations. With progressing systemic inflammation, glucose intolerance increases, with gluconeogenesis accelerated by mass action of lactate and

Table 4.8 Summary of Metabolic Changes During Trauma and Severe Systemic Inflammation in Humans

		Severe Inflammation	
Substance	**Trauma**	**EBB**	**Flow**
Adrenaline	INC	N	INC
Noradrenaline	INC	N	INC
Cortisol	INC	N	INC
Insulin	DEC	INC	VAR
Glucose	INC	VAR	VAR
Fatty acids	DEC	VAR	DEC
Albumin	VAR	DEC	DEC
Acute reactants	VAR	INC	INC
Urine nitrogen	VAR	INC	INC
Ree	VAR	INC	INC
Glucose oxidation	DEC	INC	DEC
Fat oxidation	INC	INC	INC

Abbreviations: N, normal; INC, increased; DEC, decreased; VAR, variable.

alanine. Glucose uptake is augmented, particularly at major inflammatory foci, such as a large wound. Therefore, elevated glucose production may provide an important energy substrate for inflammatory cells (52,53,55,56).

Increased lactate (lactic acid) concentrations are commonly measured when oxygen delivery is insufficient to meet cell oxygen requirements. However, in the flow phase of shock, elevated lactate has been periodically documented despite an increase in oxygen delivery and consumption. Other possible causes of elevated lactate are increased production by inflammatory cells (aerobic glycolysis) or decreased processing of pyruvate through the Krebs cycle because of enzyme abnormalities. For instance, active macrophages have been shown to increase glucose utilization, elevate lactate production, and proportionally increase pyruvate, a phenomenon seen in inflammation (40,57–59). Regardless of etiology, an elevated lactate and/or delayed lactate clearance are associated with a poor prognosis, being principal markers of the "rude unhinging" of cell metabolism during severe systemic inflammation (60,61).

Fat

Free fatty acids and triglyceride blood concentrations increase during inflammation, indicating an excess metabolic demand. The excess can result in the accumulation of fat in the liver, muscle, heart, and kidney (62).

Protein

The loss of protein (negative nitrogen balance) witnessed during the flow phase following injury continues at an accelerated rate in severe inflammation and appears to correlate well with organ failure. Since protein is essential for enzymes and coagulation protein synthesis, immunocompetence and diaphragm function, the relationship of progressive protein loss to increased morbidity and mortality is readily understandable.

The greatest protein breakdown occurs in skeletal muscle, the intestine, and connective tissue, with flux of the resultant amino acids (particularly alanine and glutamine) to the liver where protein synthesis, especially of acute-phase reactants and albumin, is increased but does not equal breakdown. Amino acids are oxidized as an energy source, especially in skeletal muscle. Increased serum alanine promotes hepatic gluconeogenesis rather than protein synthesis. Glutamine, which is important for immune cell, kidney, and intestinal mucosal cell metabolism, may be decreased in plasma despite the release from muscle.

Increased breakdown also results in ureagenesis, ammonia, and uric acid production as well as increased creatinine release. When unchecked or not ameliorated with therapy, severe protein malnutrition can develop rapidly with progressive liver dysfunction a potential terminal event (52,53,63).

Mediators of the Metabolic and Hormonal Response

The stimulation and inhibition of cellular activity that results in the metabolic and hormonal response to severe injury and inflammation can be divided into four potential pathways: the central nervous system, endocrine (interactions via the circulation), paracrine (cell-to-cell interactions), and autocrine (cell self-stimulation). All the mediators listed in Table 4.9 contribute to the observed metabolic alterations described above. No single pathway appears to be sufficient to explain the magnitude of changes measured in animals and human (55,64).

The positive and negative feedback potential within this array of biologic products is staggering. Further investigation to enhance the understanding of these complex interactions will be useful in the pursuit of knowledge. It is unlikely that this pursuit will result in a simple

Table 4.9 Mediators of Metabolism Following Severe Injury and/or Inflammation

1. CNS
   - Hypothalamus
     - ACTH
     - ADH
     - Growth hormone
     - TSH
   - Sympathetic nervous system
     - Norepinephrine
   - Endorphins
2. Endocrine
   - Adrenal cortex
     - Cortisol
     - Aldosterone
   - Adrenal medulla
     - Epinephrine
   - Pancreas
     - Insulin
     - Glucagon
   - Thyroid
     - T3
     - T4
   - Cytokines
     - IL-1
     - TNF
     - IL-6
   - Phospholipase A2
3. Paracrine
   - Cytokines
     - IL-1
     - TNF
     - IL-6
   - Prostaglandins
   - Superoxide radicals
4. Autocrine
   - Cytokines
     - IL-1
     - TNF
     - IL-6
   - Prostaglandins
   - Superoxide radicals
   - Nitric oxide

Abbreviations: ACTH, adrenocortical trophic hormone; ADH, antidiuretic hormone; TSH, thyrotropin; T3, triiodothyronine; T4, thyroxine; IL-1, interleukin 1; TNF, tumor necrosis factor; IL-6, interleukin 6.

method of therapeutic intervention that will maintain the beneficial effects of this metabolic response (e.g., wound healing, acute-phase reactant synthesis), while dramatically inhibiting the detrimental effects (muscle wasting). Instead, support of the patient to ameliorate the adverse metabolic effects while the primary inflammatory disease is addressed will likely remain the mainstay of management.

SYSTEMIC INFLAMMATION AND HOST-DEFENSE DEFICITS

An oxymoronic feature of systemic inflammation is the recognition of deficits in host-defense processes that can accompany activation of cell functions essential for wound healing and removal of non-self materials. Apparently, if either the wound is too large or the exposure to foreign materials is too noxious, then local host-defense capabilities are overwhelmed, resulting in systemic cell activation that suppresses all aspects of the host-defense mechanisms listed in Tables 4.3 and 4.4. These changes diminish an individual's capability to heal new and/or existing wounds and control new infection. The better documented deficits are listed in Table 4.10.

The importance of alterations in the gastrointestinal tract (GIT) has been continuously emphasized for at least the past three decades. Multiple experimental studies have documented GIT mucosal barrier malfunction following insults such as hemorrhage, endotoxin administration, and burn injury. Migration of bacteria, fungi, and breakdown products of microorganisms from the lumen to the intestinal lymphatics and/or portal blood has been advocated as a mechanism of stimulating ongoing systemic inflammation and the resultant organ malfunction. In addition, decreased presence and/or function of the gut-associated lymphatic tissue (GALT) have been implicated in both regional and global host-defense suppression. Importantly, ischemia/reperfusion of the GIT results in an oxidative stress response that may be particularly linked to gut lymphatic drainage as the pathway for activation of systemic inflammation (65–69).

In 1997, Roger C. Bone, a contributor to the consensus conference that defined SIRS, offered the concept of the compensatory anti-inflammatory response syndrome (CARS), to assist with the recognition and cataloging of alterations that decrease the function of the innate and acquired host defenses. Exuberant stimulation of pro-inflammatory cell activity as well as enhanced anti-inflammatory regulatory functions can result in poor outcomes. Interestingly, male gender may be particularly linked to immunosuppression following inflammatory stimulation (4,70–76).

Table 4.10 Host Defense Deficits During Systemic Inflammation

I. Barrier function—GIT
A. Migration of bacteria/fungi into lymph or portal vein
B. Apoptosis of GALT
C. Ischemia/reperfusion
II. Compensatory anti-inflammatory response syndrome
A. Cytokines
i. IL-10
ii. IL-4
iii. IL-13
iv. TNF-α receptors
v. IL-1 receptor antagonist
B. T-cell alterations
i. Anergy
ii. Inhibition of Th-1 (T helper cell-1) polarization
iii. Decreased dendritic cell function
C. PMN alterations
i. Decreased delivery to secondary inflammatory sites
ii. Decreased phagocytosis by immature neutrophils
D. Macrophage suppression

Abbreviations: GIT, gastrointestinal tract; GALT, gut associated lymphatic tissue; IL-10, interluekin 10; IL-4, interluekin 4; IL-13, interluekin 13.

SEVERE SYSTEMIC INFLAMMATION: DIAGNOSIS AND TREATMENT

Clinical Diagnosis of Severe Systemic Inflammation

The clinical manifestations of severe systemic inflammation (Table 4.11) are as potentially varied as the many organs that may manifest malfunction. Most patients will demonstrate hemodynamic alterations, but sometimes abnormal lung, central nervous system, hematologic, and/or other organ states represent the primary evidence of systemic inflammation rather than hemodynamic changes. Therefore, a high index of suspicion of the patient at risk, augmented by evidence gathered during physical examination and selected laboratory tests will support the diagnosis of inflammation sufficient to threaten vital organ function and/or life.

The Patient at Risk

The first category of risk is that a patient has recently acquired a disease (e.g., severe pancreatitis) or sustained an injury (e.g., unstable pelvic fracture with ruptured spleen) that is characterized by marked inflammatory cell activation. The second category of risk is that a patient has an underlying condition (e.g., immunosuppression following liver transplantation) or recent procedure (e.g., elective colon resection for carcinoma) that makes a new infectious threat more likely. In addition, any patient who has suffered a life-threatening episode of hypoperfusion (e.g., cardiogenic shock following an acute myocardial infarction, upper gastrointestinal hemorrhage sufficient to result in hypotension) is also at risk for developing systemic inflammation either at the time of the hypoperfusion/reperfusion or days later from new insults (e.g., infection, recurrent hemorrhage, wound dehiscence).

Physical Examination

Vital Signs

Usually, severe systemic inflammation is manifested as a decrease in blood pressure (vasodilation, increased venous capacitance), an increase in heart rate (increased catecholamine concentrations), an increase in respiratory rate (mediator-induced lung injury), and an elevated temperature (IL-1, IL-6, TNF α). Patients with underlying cardiac disease may present with hemodynamics more consistent with congestive heart failure (elevated blood pressure and tachycardia). Hypothermia (decreased oxygen consumption and heat production—Ebb phase of shock) and hemodynamics consistent with cardiogenic shock may be present in the most severe cases.

General Overview

The patient is usually restless and may demonstrate mental status alterations ranging from delirium to coma (77). In fact, mental status changes may precede obvious hemodynamic and/or respiratory findings. This sometimes leads to misdirection in evaluation (computed tomography of the brain). Such alterations in central nervous system (CNS) function are rarely focal and most consistent with a metabolic encephalopathy.

Table 4.11 Common Clinical Manifestations of Severe Inflammation

1. Vital signs
   - Temperature elevation, hypothermia when severe
   - Tachycardia
   - Tachypnea
   - Hypotension with warm or cold extremities
2. Change in mental status
3. Respiratory insufficiency
4. Ileus
5. Oliguria, increased urine protein
6. Elevated hemoglobin, thrombocytopenia leukocytosis, leukopenia when severe
7. Increased serum glucose, decreased ionized calcium, increased serum lactate/lactic acid

If intravascular volume is decreased, the skin will be cool, possibly mottled, with vasoconstriction most often evident in both the upper and lower extremities. Capillary refill will be decreased. If intravascular volume is normal, then the skin can be warm and pink (78).

Lungs

The lung examination may demonstrate clear lungs [even with acute respiratory distress syndrome (ARDS)—see chapter 6, The Pulmonary System] but may also exhibit rales, rhonchi, and bronchospasm. Examination findings consistent with consolidation (e.g., tubular or tubulo-vesicular breath sounds, egophony) may assist in locating an inflammatory process, but are clearly not peculiar to systemic inflammation. The lung examination is not sufficiently specific to make a diagnosis of systemic inflammation or other etiology of diffuse pulmonary malfunction.

Cardiovascular Examination

Hypotension and tachycardia are usually present along with crisp heart tones. After intravascular volume restitution, extremities are characteristically warm, demonstrating good capillary refill. Hypotension with warm hands and feet usually indicates the vasodilation (nitric oxide) response to inflammation, although anaphylaxis and a high spinal cord injury could produce similar findings. Jugular venous pressure will be low by clinical examination.

As a result of plasma exudation and other causes of plasma volume loss, sequestering of fluid usually occurs in the patient. This can be sudden or, if the patient has been monitored in a hospital setting, the positive fluid balance and an increase in weight may have been documented for several days prior to an acute deterioration.

Myocardial depression from inflammation might result in an elevated jugular venous pressure as well as hypertension and an S3 gallop (see chap. 3 and section on "Myocardial Depression"). Severe myocardial depression sufficient to result in hypotension and a clinical picture identical to cardiogenic shock is possible. However, such myocardial malfunction is much less common than are circulatory deficiencies secondary to hypovolemia. The clinician must be extremely careful to distinguish the fluid sequestration and positive fluid balance of severe inflammation from the same phenomena seen with cardiogenic states. Treating hypovolemia with fluid restriction and diuretics will result in further circulatory embarrassment.

Decreased urine output secondary to severe inflammation is common and most often secondary to inadequate cardiac output from hypovolemia. A cardiogenic pre-renal state is also possible, as is toxin-induced intrinsic renal injury. Regardless of etiology, persistent oliguria (for hours) can be an early indicator of systemic inflammatory threat.

Abdominal Examination

Abdominal distention, decreased or absent bowel sounds, and tympany may accompany any severe inflammatory process and represents the ileus that can develop with or without a primary disease or injury in the abdominal cavity. Obviously, if the principle site of inflammation is in or near the abdominal cavity, then examination might provide more specific evidence of a primary focus (peritonitis on physical examination, cellulitis in the flank, etc).

CNS Examination

As stated above, mental status changes are common and usually non-focal, consistent with a metabolic encephalopathy (see chap. 9).

Laboratory Studies

Hematologic

An increase in total white blood cell count, particularly immature PMNs, is most common. Leukopenia denotes more severe disease and usually exhibits a high concentration of immature PMNs. Leukopenia appears to be secondary to diffuse tissue infiltration rather than bone marrow

suppression (51). The platelet count usually decreases and evidence of consumption of coagulation proteins with breakdown of fibrinogen (increased prothrombin time, increased partial thromboplastin time, and increased fibrin spit products or D-dimer) also denotes more severe disease (79). Hemoglobin may increase as plasma volume is threatened by "third space" accumulations. Such an increase can be a useful tool in assessing intravascular volume resuscitation since plasma volume is likely to be inadequate until the hemoglobin has at least returned to the patient's baseline value.

Lung Studies

A decrease in arterial pO_2 and pCO_2 is characteristic of severe systemic inflammation as well as many other lung disease states (78). A chest X-ray may be clear and/or demonstrate loss of lung volume as well as evidence of pulmonary fluid accumulation, most often from a noncardiogenic pathophysiology (see ARDS in chap. 6). The clinician should recognize that respiratory symptoms, signs, and laboratory data during severe inflammation may be indistinguishable from those seen commonly in CHF, and should be alert to the dangers of the misdiagnosis and management of severe inflammation effects on the lung as CHF (see chaps. 3 and 6).

Urine Studies

As stated above, oliguria is common during severe inflammation and is most often secondary to an inadequate circulation, resulting in laboratory tests consistent with a pre-renal state (e.g., elevated urine specific gravity, low urine sodium, increased urine osmolality, elevated blood urea nitrogen/creatinine ratio).

Dating from at least the time of Meleney's description of synergistic bacterial gangrene, increased urine protein has been witnessed during severe inflammatory conditions. Therefore, it is possible that renal microvasculature (glomerular or otherwise) respond to the same mediators that result in increased capillary permeability elsewhere. Increased urine protein excretion may indicate that systemic inflammation is present, especially when no local renal disease (i.e., glomerulonephritis) is evident (see chap. 7) (27,80).

Serum Chemistries

Elevated blood glucose is common during inflammation (see Metabolic and Hormonal Response section above). Decreased total serum calcium has been recognized for many years to be associated with one particular severe inflammatory disease—pancreatitis—and the extent of decrease correlates with the severity of disease. Ionized calcium represents the calcium that is not bound to albumin and is not, therefore, influenced by albumin concentrations, which can change significantly during critical illness. Ionized calcium is also better correlated with parathyroid hormone release as compared with total calcium.

Ionized calcium decreases with any disease that causes either severe hypoperfusion or inflammation. In addition, the magnitude of decrease correlates with the severity of disease. While not specific for inflammation, ongoing severe inflammation must be considered possible in any patient with decreased ionized calcium. In contrast, normal ionized calcium would be unusual during severe inflammation and/or hypoperfusion. Therefore, a normal value would suggest that a severe systemic insult is not present (81–83).

Electrolyte and/or arterial blood gas information consistent with metabolic acidosis and an elevated lactic acid level are often seen in severe inflammation, with greater acidosis and higher lactic acid levels associated with poor outcome. Like ionized calcium, these abnormalities do not distinguish severe inflammation from a decrease in either regional or global perfusion (see chap. 2). Metabolic acidosis could mean that either disease is present and should prompt further diagnostic efforts (60,84–86).

Markers of Severity (Table 4.12)

As mentioned in the description of SIRS, this diagnostic listing did not provide specific criteria for mild, moderate, and severe systemic inflammation, despite including two alterations (hypothermia and leukopenia) indicative of advanced illness. Since shock is the principle etiology of multisystem

Table 4.12 Markers of Severe Shock (Systemic Inflammation and Hypoperfusion)

I. Bedside evaluation—clinical consistency with the Ebb phase
   A. Hypotension
   B. Tachycardia
   C. Hypothermia
   D. Vasoconstriction
   E. Delirium
   F. Oliguria
II. Common laboratory studies : can be present in the Ebb and Flow phase
   A. Leukopenia
   B. Thrombocytopenia
   C. Metabolic acidosis
   D. Increased lactic acid
   E. Decreased ionized calcium
III. Organ failure scores—usually measured in the Flow phase
   A. MODS score
   B. SOFA score
IV. Less common laboratory studies—measured in both Ebb and Flow phases
   A. Oxygen consumption
   B. Cellular injury score
   C. Mediator concentrations

Abbreviations: MODS, multisystem organ dysfunction score; SOFA, sequential organ failure assessment score.

organ failure, the use of organ failure ranking has been used to catalog severity of disease, whether the organ threats appear to develop principally from hypoperfusion or systemic inflammation. Because these two processes are impossible to completely separate, markers of severity can be practical for the evaluation of both etiologies (42,44,45,48,78,84,87–94).

TREATMENT

Achieve an Excellent Circulation Quickly

Rapid resuscitation of the circulation (achieving goal-directed endpoints within six hours of Emergency Department admission) has been documented to reduce the mortality for patients suffering from severe sepsis and septic shock (95). Importantly, the blood concentrations of pro-inflammatory mediators are diminished in patients who rapidly achieve the goal-directed endpoints (18). Faster restoration of the circulation has also been an advantage in acute pancreatitis (96). These human data vigorously support the linkage between hypoperfusion and inflammation. As in experimental conditions, rapid restoration of sufficient oxygen delivery to meet metabolic demand in humans results in a decreased systemic inflammation (17,18).

Since at least the 1980s, the definition of end-points for circulation resuscitation has been controversial (Table 4.13), especially when restoration of plasma volume does not result in a hyperdynamic (Flow Phase) circulation. A complex mix of perioperative and other adult intensive care unit (ICU) patients have been studied, usually after ICU admission. A common theme in many studies is that patients who increase oxygen consumption in response to increased oxygen delivery are more likely to survive (43,44,97,98). In other words, the hypermetabolic state of the Flow Phase is associated with improved outcomes.

Since oxygen consumption is not easy to measure, the relationship between delivery and consumption, as reflected in venous oxygen saturation, has been used as a surrogate. Regardless of concerns for the precision of this monitor, central venous oxygen saturation measurement has proven sufficiently practical to become the recommended initial tool (99,100).

Like the common theme related to increasing oxygen consumption, decreasing blood lactic acid concentration is also associated with survival. Whether improvement in this metabolic marker is strictly connected to improved oxygen metabolism or is a more generic indicator of the inflammatory state is moot (95,99,101).

As mentioned in the Shock chapter, ionized calcium is a useful marker of severity early during acute illness, with the lowest values associated with the greatest mortality. While low

Table 4.13 End Points of Resuscitation

I. Circulation measures
A. Cardiac index
B. Oxygen delivery
C. Mixed venous oxygen saturation
D. Central venous oxygen saturation
E. Urine output >0.5 CC/KG/HR
F. Central venous pressure
II. Metabolic measures
A. Lactic acid
B. Oxygen consumption
C. Ionized calcium

ionized calcium usually increases during the first days of surgical critical illness, no one has compared the rate or magnitude of ionized calcium change and survival (81). Therefore, ionized calcium has not been used as a parameter to guide resuscitation.

Even more controversial than determining resuscitation goals is the methods employed to meet the end-points selected (Table 4.14). While the general consensus is that plasma volume expansion with either crystalloid or colloid is acceptable, colloid materials such as albumin, dextran, gelatin, and hydroxyethyl starch are not only more expensive but may have particular dose-related side effects such as coagulopathy and renal failure (102–105). The only regularly measured advantage from colloid administration is less total volume administration.

The principal crystalloid solutions are 0.9% saline [commonly termed normal saline (NS)], lactated Ringer's solution (LR), and hypertonic saline (HTS). In the past, LR was compounded using both the D and L isomers of lactate and the D isomer was found to augment pro-inflammatory processes. In 1999, the Institute of Medicine (IOM) recommended that the D isomer be removed, leaving the L isomer that did not exhibit these pro-inflammatory properties (106). HTS also appears to have an anti-inflammatory effect and the combination with dextran (HTS-D) has been repeatedly investigated with no overall benefit documented. Use of large volumes of NS and use of HTS are associated with hyperchloremia and a non-anion gap acidosis that can make use of arterial pH and base deficit measurements more difficult to interpret (107). Therefore, at present, LR with the L isomer is the preferred crystalloid (106).

Red cell transfusion for blood volume expansion (higher than hemoglobin of 7 g/dL) is even more problematic (see chap. 10). However, especially in severe systemic inflammation, increasing oxygen delivery by increasing blood oxygen content with red cell transfusion has not been associated with a documented increase in oxygen consumption (108–111).

Most patients with systemic inflammation will achieve a hyperdynamic, Flow Phase, circulation with restoration of blood volume. When evidence of inadequate oxygen delivery persists (Ebb Phase) despite what is deemed a sufficient blood volume, then the use of inotropic support is indicated for what presumably is a cardiogenic state of hypoperfusion induced by inflammation-associated myocardial depression. Today, the common prompt for inotropic agent administration is continuation of a low central venous saturation (<70%) and/or an elevated lactic acid (>4 mmol/L). Measurement of a low cardiac index (<2.5 L/min/m^2) and an echocardiogram showing poor ventricular function would also support the addition of inotropic therapy. Typically, dobutamine is recommended, but a phosphodiesterase inhibitor such as milrinone can also be effective (100,112).

The general recommendation for vasoconstrictor (norepinephrine, dopamine, phenylephrine, or vasopressin) infusion is to achieve a mean arterial pressure (MAP) ≥65 mm Hg when fluid infusion does not meet this parameter. Increasing MAP to levels higher than 65 mm Hg has not been shown to be beneficial and may be detrimental (113–115). Typically, these vasoconstrictor drugs have been used when cardiac output is high and hypotension is secondary to low systemic resistance rather than low cardiac output. Under these circumstances, vasoconstriction is not harmful and the choice of agent(s) is dependent more on idiosyncrasy rather than documented advantage. For instance, dopamine is associated with more arrhythmias (116–119).

Table 4.14 Treatment of Severe Inflammation

Achieve an excellent circulation quickly
Controversies in management
I. Restore blood volume
A. Crystalloid
B. Colloid (including red cells)
II. Augment flow
A. Restoration of plasma volume only
B. Inotropes
i. Dopamine
ii. Milrinone
iii. Dobutamine
III. Augment pressure
A. Dopamine
B. Norepinephrine
C. Phenylephrine
D. Vasopressin
E. Calcium
F. Hydrocortisone

While intravenous calcium administration may increase blood pressure and cardiac output, administration of calcium has not been shown to be a benefit in experimental studies (120–122).

Hypotension (MAP <65 mm Hg) that persists despite the use of vasoconstrictor medications may respond to the administration of hydrocortisone (<300 mg/day). The benefit of hydrocortisone administration may be particularly evident when vasopressin is used to increase systemic resistance (100,123). Glucocorticoid use for systemic inflammation is further discussed in the section on "Inhibition of Inflammation Mechanisms".

Source Control: Treat the Underlying Cause

Once severe inflammation is recognized and circulatory deficits addressed, the next or concomitant principle of treatment is to discover the underlying cause and initiate appropriate therapy (100). While infection is the most common cause of severe systemic inflammation, tissue injury without infection (i.e., severe pancreatitis, multiple trauma), and other non-infectious threats such as reactions to drugs and/or transfusions, can result in severe systemic inflammation indistinguishable from that seen with the invasion of microorganisms. The management guidelines for common inflammatory conditions in surgery are presented in the individual organ-related sections in this manual.

Inhibition of Inflammation Mechanisms

Unfortunately, sometimes systemic inflammation continues despite adequate restoration of the circulation and treatment of the initiating insult. In some patients, inflammation appears to become self-sustaining, as if a positive feedback system has developed in one or more organ. As describe previously, such persistence of the Flow Phase of shock can result in multisystem organ failure and death, more likely from the toxic effects of systemic inflammation rather than oxygen delivery deficits.

Many therapies focused on specific mediators of inflammation have not proved beneficial in humans (124–130). Instead, management strategies that inhibit several of the overlapping and redundant pro-inflammatory pathways seem to offer greater potential for benefit.

As stated previously, inflammation has beneficial effects (e.g., wound healing, defense against invasive organisms) that are important for survival during critical illness. Therefore, a successful outcome depends greatly on a balance between the beneficial and detrimental effects of inflammation. Therapy that aggressively suppresses inflammation (i.e., pharmacologic

doses of anti-inflammatory steroids) may result in short-term advantages, such as hemodynamic and pulmonary function improvement, but suppression of the beneficial effects of inflammation may result in death secondary to recurrent infection or wound breakdown.

With all treatments designed to limit severe inflammation, this balance between detrimental and beneficial effects for both the short term (hours to days) and long term (days to weeks) must be evaluated. The use of steroids for severe inflammation is particularly illustrative of the difficulties with this balancing process.

Alterations in adrenocortical function following severe hemorrhage and inflammation have been recognized for many years. For most patients, an elevated blood cortisol level is considered part of the normal response to a severe stress that resulted in ICU admission. However, some stressed patients may have depressed adrenocortical function, exemplified best by cases of meningococcal bacteremia with adrenal hemorrhage, and other cases of anatomical disruption of adrenal tissue. Over the past several decades, measurement of lower than expected blood cortisol concentrations during severe inflammation, without anatomic alterations of the adrenals, has prompted speculation that severe inflammation may result in a pathophysiologic suppression of adrenal function from mechanisms such as TNF and IL-1 interference with adrenal cortisol synthesis. Therefore, severe inflammation may be associated with downregulation of an endogenous negative feedback system that would serve to check the progress of pro-inflammatory activation.

Administration of pharmacologic doses of anti-inflammatory steroids demonstrated acute beneficial effects in the experimental models of septic shock and adult respiratory distress syndrome. The short-term benefits documented in these experimental studies did not prove transferable to long-term benefits in humans (131). As stated above, the known adverse effects of pharmacologic steroids on host defenses and wound healing may have disrupted the proper balance between the detrimental and beneficial effects of inflammation.

For all therapies listed in Table 4.15, this balance must be considered. The benefits of inflammation are primarily realized at local sites (the focus of tissue injury or infection). The detrimental effects are primarily systemic (e.g., alterations in circulation, pulmonary function). Therapies that allow local inflammation to continue while the systemic inflammation is suppressed may improve the local/systemic inflammatory balance.

The administration of physiologic doses of hydrocortisone may be just such a titratable anti-inflammatory agent, in keeping with what Beisel termed the "eucorticoid" state (131,132). When severe inflammation is associated with or without less than expected blood cortisol concentrations, several studies have reported improved hemodynamic and pulmonary function when low-dose (150–300 mg/day) hydrocortisone is administered (100,133–139). In addition, since exuberant inflammation can suppress host defenses, the administration of physiologic hydrocortisone during severe inflammation may actually enhance host defense (140).

Recombinant human-activated protein C ameliorates the procoagulant features of active inflammation and, thereby, can inhibit multiple inflammatory pathways. Current recommendations are linked to improved survival in a subgroup analysis for patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥25 (severe illness). The principal risk is bleeding that is more problematic in surgical patients and those with invasive procedures (100,141).

While oxidative stress is an important feature of severe systemic inflammation, attempts to limit the generation and/or the effect of ROI have met with limited success. Studies of the administration of mannitol, folate, vitamin C, and vitamin E have supported a beneficial effect. Recent interest in selenium, sodium-hydrogen exchange inhibition, and adenosine highlights the ongoing attempts to ameliorate this prominent process of inflammation-associated cell and organ insults (142–147).

Drugs used to treat cholesterol (statins) have been shown to have important anti-inflammatory properties that may provide benefit during systemic inflammation (148).

Immunologic Enhancement

As mentioned above, unchecked severe inflammation may be secondary to deficient host defenses present either before the inflammatory insult or developing as a result of the inflammatory

Table 4.15 Inhibition of Inflammation Mechanisms

1. Glucocorticoids—physiologic dosing
2. Recombinant human activated protein C
3. Antioxidants
   A. Mannitol
   B. Vitamin C
   C. Vitamin E
   D. Selenium
   E. Allopurinol
   F. N-acetylcysteine
   G. Folate
4. Inhibition of ischemia/reperfusion injury
   A. Antioxidants as above
   B. Na-H-exchange inhibition
   C. Adenosine
5. Statin administration

Abbreviation: Na-H, sodium hydrogen.

Table 4.16 Immunologic Enhancement in Critically Ill Surgical Patients

1. Maintain an excellent circulation
2. Source control
3. Nutritional support—preferably enteral versus TPN
4. Proper use of antibiotics
5. Immunoglobulin administration

Abbreviation: TPN, total parenteral nutrition.

response. Persistent deficits in host defenses are associated with increased infection and mortality risk in critically ill surgical patients. Strategies for improving host defenses are several (Table 4.16) but center on the principles of effective management of severe systemic inflammation along with the use of enteral feedings. Limiting antibiotic use can diminish the emergency of multi-drug resistant organisms. Immuno-enhancing diets (see chap. 8) and immunoglobulin administration are directed at improving host defense (149,150).

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5 | The critical surgical abdomen

DEFINITION

For this manual, the critical surgical abdomen is defined as abdominal insults and/or pathophysiological sequelae that result in an open abdomen in the intensive care unit. The principal processes associated with the critical surgical abdomen are damage control laparotomy (DCL) and the abdominal compartment syndrome (ACS).

DAMAGE CONTROL LAPAROTOMY

Most often DCL is employed in the setting of trauma, but non-trauma insults can result in a similar plan of management (Table 5.1). The use of DCL is linked to the concept of damage control resuscitation (DCR), whereby the life-threatening abdominal condition demands simultaneous attention to measures that can limit the state of shock and the consequent cell and tissue injuring effects of too little oxygen delivery and too much inflammatory toxin (see chap. 2).

Damage Control Resuscitation

The principal features of DCR are listed in Table 5.2. These features address the components of the "bloody vicious cycle," also called the "triangle of death"; these are coagulopathy, acidosis, and hypothermia (1,2). While these threats are most often linked to severe trauma, severe systemic inflammation can result in the same alterations, albeit without the loss of red cells from the circulation.

Periodically, these alterations result in a self-perpetuating pathophysiology that will not respond to ongoing operating room management. Survival depends upon interrupting the "bloody vicious cycle." DCR as well as damage control surgery (DCS) serve to accomplish that task (3).

The combination of data gathered in recent military conflicts and civilian experience supports the early administration of fresh frozen plasma (FFP) and platelets for patients suffering with life-threatening hemorrhage resulting from trauma. While the abdominal cavity is the primary site for bleeding of this magnitude, the same advantage is anticipated for patients with chest, pelvic, and/or extremity injuries (3,4).

Anticipation of coagulopathy is important, especially since FFP must be thawed before administration. For trauma, the report of persistent hypotension in the field and during transport as well as hypotension and initiation of blood transfusion at a referring facility can serve as sufficient prompts to initiate a massive transfusion protocol that includes early release of FFP and platelets. In the Emergency Department, hypotension (<110 mm Hg) and a positive focused assessment with sonography for trauma (FAST) for abdominal fluid are indicative of life-threatening hemorrhage. Similarly, hypotension with a pelvic fracture and evidence of active hemorrhage on computed tomography (CT) scan or active bleeding in the thoracic cavity can prompt early use of FFP and platelets.

Acidosis at or below a pH of 7.2 can result in hemodynamic and coagulation disturbances. The principal etiology is inadequate oxygen delivery to meet cellular oxygen demand resulting in anaerobic glycolysis and lactic acid production. In addition, the use of large volumes of 0.9% saline often results in a hyperchloremic state that can aggravate metabolic acidosis (see chap. 7) (3).

Despite the known adverse effects from inadequate oxygen delivery, some aspects of resuscitation management remain controversial, especially the timing and completeness of reversing oxygen supply deficits prior to control of active hemorrhage. While the magnitude and duration of inadequate oxygen delivery and the resultant oxygen debt have been shown to be directly associated with the severity of cell and organ injury (see chap. 2), vigorous resuscitation to normal hemodynamic values may exacerbate uncontrolled hemorrhage.

Permissive hypotension (systolic blood pressure ≤85 mm Hg) is the strategy employed to allow some improvement in oxygen delivery while not accentuating hemorrhage. Using this

Table 5.1 Damage Control Laparotomy Common Related Conditions

I. Trauma
II. Ruptured abdominal aneurysm
III. Severe abdominal sepsis
IV. Bowel ischemia/infarction

Table 5.2 Principal Considerations for Damage Control Resuscitation

I. Augmentation of coagulation (mostly for hemorrhage)
A. Anticipation of coagulopathy
B. 1:1 Ratio of FFP to RBCs
C. 1:1 Ratio of platelets
II. Augmentation of the circulation (for hemorrhage and inflammation)
A. Reversal of acidosis
B. Permissive hypotension
III. Management of hypothermia (for hemorrhage and inflammation)
A. Warm blankets
B. Warmed IV fluid and blood products
C. External warming device
D. Body cavity lavage with warmed saline
E. Extracorporal blood warming

Abbreviations: FFP, fresh frozen plasma; RBCs, red blood cells; IV, intravanous.

subnormal endpoint of resuscitation, fluid and blood product administration is provided in small volumes, or not at all, until definitive control of the bleeding site is accomplished. This strategy can support perfusion of vital organs while limiting ongoing blood loss from uncontrolled injuries.

The application of permissive hypotension is best supported in the setting of penetrating injury, particularly cardiac wounds, and with short pre-hospital transport and, thereby, short preoperative times. At present, no consensus guidelines are available for other trauma or hemorrhagic conditions, but a similar approach would seem applicable to isolated extremity hemorrhage or ruptured intra-abdominal aneurysm (3,5).

The management of hypothermia, especially in trauma patients, is not controversial. Preventing and reversing hypothermia is a consideration that must begin in the field and continue from the Emergency Department, to the operating room, and into the intensive care unit. Warm blankets, warmed fluid and blood products, external warming devices, lavage of body cavities with warm saline, and extracorporal blood warming have all been effectively utilized, demonstrating that warming is beneficial to overall patient outcome. The method(s) employed should be linked to the severity of the hypothermia and the associated physiologic derangements. The most rapid and aggressive technique is extracorporal blood warming (6–9).

Damage Control Laparotomy

The components of DCL are listed in Table 5.3. DCL may be planned at the outset of abdominal exploration or may become a requisite as the "bloody vicious cycle" blossoms during the surgery. Packing is the usual first step for hemorrhage control, with attention subsequently directed to "surgical" bleeding, that is, sites that can be readily addressed by clamping, ligation, and sometimes removal. In blunt trauma, the surgical sites will most often be the spleen and mesenteric vasculature. For penetrating trauma, any site may demand a direct approach, with ligation of venous structures and shunting versus repair of arterial structures. Recognition of hemorrhage at sites not amenable to direct surgical approach (pelvic and deep hepatic regions) can prompt on-table angioembolization. If on-table angioembolization is not an option, then abdominal packing for hemorrhage control, temporary coverage of the abdominal viscera, and transport to the angiography suite should be considered (3).

Table 5.3 Components of Damage Control Laparotomy

I. Stop Hemorrhage
A. Packing
B. Ligation
C. Organ extraction
D. Arterial shunts
E. On table angioemoblization
II. Control contamination
A. Suture
B. Staple
C. Excision
D. Tube drainage
III. Open abdomen
A. Temporary skin closure
B. Plastic with homemade suction
C. Temporary abdominal wall substitute
D. Vacuum devices

Table 5.4 Grading of Intra-Abdominal Hypertension

Grade	Pressure (mm Hg)
I	12–15
II	16–20
III	21–25
IV	>25

Control of a perforated hollow viscus may be achieved with sutures, staples, or resection of the site with plan for delayed re-establishment of intestinal continuity. Intraluminal tube drainage is another option if tissue cannot be apposed.

The options for leaving the abdomen open are several, from closing the more mobile skin with towel clips to the application of a vacuum device. No clinical data support one choice over the other (10). Interestingly, peritoneal negative pressure therapy seems more effective in a model of intraperitoneal sepsis, possibly by removing inflammatory ascites (11).

THE ABDOMINAL COMPARTMENT SYNDROME

Definition and Etiologies

In 2004, the World Society of the Abdominal Compartment Syndrome developed a consensus definition that included the following: intra-abdominal hypertension (IAH) as an intra-abdominal pressure (IAP) ≥12 mm Hg and ACS as a sustained IAP ≥20 mm Hg that is associated with new organ dysfunction or failure. In addition, abdominal perfusion pressure (APP) was defined as mean arterial pressure (MAP) minus IAP (12). APP <60 mm Hg is worrisome for ACS even when IAP is <20 mm Hg (13).

IAH has been catalogued into four grades on the basis of measured pressure (Table 5.4) (12). ACS has been classified as either primary (a result of intra-abdominal or retroperitoneal pathology) or secondary (a result of abdominal region edema and/or ascites related to resuscitation). Common etiologies of primary and secondary ACS are listed in Table 5.5.

IAP is usually measured using the urinary bladder via a Foley catheter (14,15).

Pathophysiology (Table 5.6)

IAH can result in a decrease in cardiac output, principally by impaired venous return (see chap. 3). The increase in intrathoracic pressure from IAH results in an extraluminal increase in

Table 5.5 Common Etiologies of Primary and Secondary Abdominal Compartment Syndrome

I. Primary
A. Abdominal trauma
B. Retroperitoneal trauma/hemorrhage
C. Pancreatitis
D. Abdominal sepsis
E. Ischemia/reperfusion of the GIT
II. Secondary
A. Sepsis resuscitation
B. Burn resuscitation
C. Hemorrhage resuscitation – bleeding neither into nor near the abdominal cavity

Table 5.6 Pathophysiology of Abdominal Compartment Syndrome

I. Decreased cardiac output
A. Decreased venous return
1. Extraluminal increase in CVP
2. Compression of large veins in abdomen and chest
B. Decreased ventricular compliance and contractility
C. Increased systemic vascular resistance
II. Decreased regional blood flow
A. Renal
B. Gastrointestinal
C. Cerebral
III. Decreased pulmonary function
A. Atelectasis
B. Decreased compliance

central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) that could be mistakenly interpreted as excess of intravascular volume if ACS is not considered early in the workup of cardiac compromise. Because the circulatory deficit in IAH results from decreased venous return, augmenting intravascular volume in spite of an elevated CVP and PAOP can result in at a transient increase in cardiac output (16,17). After the ACS is in place, then continued blood volume expansion may be ineffective (18,19). In addition, IAH can threaten cardiac output by increasing systemic vascular resistance as well as the potential for a more direct cardiac wall effect (17,18).

Regional hypoperfusion can be greater than the effect on systemic flow, and this hypoperfusion is worsened by hypovolemia. Regional hypoperfusion is most evident in the kidneys and the gastrointestinal tract (GIT). Increased renal vascular resistance and compression of the renal vein impair renal blood flow, stimulating renin release, and aldosterone secretion (17,20). Arterial inflow to the GIT (celiac and superior mesenteric artery) is compromised and venous resistance is increased, resulting in threats to the hollow viscera and the liver (16–18,21–23).

An increase in thoracic pressure from IAH can also result in an elevated intracranial pressure (ICP) with the potential of decreased cerebral perfusion from impaired venous return. Therefore, ACS designation (impaired organ function) could include evidence of sustained intra-cerebral pressure elevations (17,18).

Pulmonary function is hampered by diminished thoracic compliance and atelectasis that result in elevated inspiratory pressures, poor oxygenation, and decreased carbon dioxide elimination (18).

Diagnosis of ACS

As stated above, the diagnosis of ACS demands the measurement of increased abdominal pressure as well as documentation of associated organ malfunction. While grade IV (>25 mm Hg)

Table 5.7 Management of Increased Abdominal Pressure

I. Drain abdominal fluid
II. Decompress distended viscera
III. Paralysis
IV. Increase MAP and APP with vasoactive drugs
V. Decompressive laparotomy

abdominal hypertension would usually be sufficient to identify ACS and prompt intervention, not all patients need to attain this magnitude of IAH to benefit from abdominal decompression. The abdominal perfusion pressure (APP) calculation can be utilized to relate the severity of circulatory threat to abdominal organs by comparing the magnitude of intra-abdominal hypertension to the systemic mean arterial pressure (MAP). For patients with a low MAP, intra-abdominal pressures <25 mm Hg can be detrimental. An APP <50 mm Hg has been shown to correlate with a poor outcome (24), whereas maintaining an APP ≥60 mm Hg has been associated with an improved outcome (13). Therefore, measurement of IAH (abdominal pressure ≥12 mm Hg) and an APP <50 mm Hg with evidence of associated organ malfunction can be sufficient to meet the definition of ACS.

Management of Intra-abdominal Hypertension

Strategies to consider when increased abdominal pressure is measured are listed in Table 5.7. All except decompressive laparotomy can be employed before the ACS is established. Abdominal fluid accumulation can develop with primary and secondary etiologies of ACS. Percutaneous drainage can be effective and less morbid than decompressive laparotomy. Attempts to decompress the intestinal tract are principally limited to the markedly distended colon. Paralysis can be effective, especially in agitated patients developing respiratory compromise, even when on a ventilator. More controversial is using vasoactive drugs to increase MAP and APP. When hypotension is secondary to decreased systemic resistance rather than insufficient cardiac output, then vasoconstrictor therapy is usually not harmful. This is less likely when hypotension is secondary to decreased cardiac output (see chaps. 3 and 4), which is the most common alteration in ACS (25).

Indications for an Open Abdomen

The indications for an open abdomen are fundamentally three: (1) damage control laparotomy; (2) anticipation of the abdominal compartment syndrome; (3) treatment of the abdominal compartment syndrome. The treatment of ACS that does not respond to less invasive measures is decompressive laparotomy, often accomplished in the intensive care unit rather than the operating room.

MANAGEMENT OF THE OPEN ABDOMEN

Management of the open abdomen (OA) can be considered in phases that may take place in a surgical critical care environment (Table 5.8). By definition, the OA does not allow fascial closure. Temporary coverage of abdominal viscera with skin is sometimes feasible, but the use of skin flaps for closure can compromise the viability of the skin and result in more tissue loss. Suturing inexpensive clear plastic materials to the skin or fascia is practical if short-term coverage is necessary, but is not durable for circumstances of repeat application and does not provide for evacuation of intra-abdominal fluid. Non-commercial and commercial suction application systems promote evacuation of intra-abdominal fluid but must be reapplied with each abdominal exploration. However, whether these improve the primary closure frequency is controversial (26,27).

Use of thicker and stronger plastic materials for stitching the fascia provides the potential for limiting fascial separation and improving sequential fascial approximation. Polypropylene

Table 5.8 Management of the Open Abdomen

I. Temporary cover techniques
A. Towel clips on skin – not advocated
B. "bogata bag" – suture of plastic to skin or fascia to cover abdominal contents
C. Vacuum application
1. Non-commercial
2. Commercial
D. Abdominal wall substitute
1. Wittmann patch
2. Non-absorbable mesh
II. Acute durable closure – fascia
A. Primary fascia
1. Resolution of tissue edema
2. Wittmann patch – gradual approximation
3. Abdominal reapproximation anchor system (ABRA)
B. Biological mesh – acceptance of a delayed hernia repair
C. Absorbable mesh – acceptance of a delayed hernia repair
D. Component release
III. Acute durable closure – skin
A. Skin graft to granulation
B. Skin flaps
C. Skin approximation devices

and expanded polytetrafluoroethylene abdominal wall substitutes are not designed for repeat exploration and are associated with high fistula rates. The Wittmann patch is designed to be readily opened and tightened as the abdominal edema subsides. None of these plastics should be considered "durable" closure alternatives and must eventually be removed, either at the time of primary fascial closure or during placement of a more long-lasting substitute (26,27).

When the abdominal alterations either resolve or fail to improve further, the options for a more "durable" fascial closure are several. Primary closure is the obvious preference and is most often achieved following trauma and in the setting of anticipation of the ACS rather than the treatment of the ACS with emergent decompression. Early primary closure may be assisted by use of neuromuscular blocking agents in the first 24 hours after DCL (28).

Both the Wittmann patch and the abdominal reapproximation anchor system (ABRA) are designed to allow repeat exploration and gradual reapproximation of fascia, presumably augmenting primary closure (26,29). Biological mesh (human, bovine, porcine) has the advantage of better "incorporation" into living tissue as compared to plastic prosthetics, but has been associated with abdominal wall laxity and may provide little long-term benefit as compared to the use of absorbable mesh. Both biologic and absorbable mesh application necessitate a skin closure plan, either full thickness or skin grafting. The acute use of component separation for primary fascial closure is controversial. It is a common method for primary closure in the "planned" ventral hernia repair that follows absorbable mesh closure (27).

Full-thickness skin closure is most common at the time of primary fascial closure. Skin approximation accompanies the reduction in the fascial defect using the ABRA and Wittmann patch systems. The use of a fascial substitute (i.e., mesh) is usually associated with equal, if not greater, separation of the skin edges. Raising local skin flaps and skin grafting to healthy granulation tissue are commonly employed. Skin approximation devices such as the Derma-Close system may also promote the success of full-thickness skin coverage (30).

MANAGEMENT OF THE ABDOMINAL VISCERA

DCL and the resulting open abdomen are associated with abdominal visceral conditions that can demand both short-term and long-term surgical attention (Table 5.9). Repetitive attention to hemorrhage control may be necessary, especially following liver trauma. Debridement of

Table 5.9 Damage Control Laparotomy and Abdominal Visceral Conditions

I. Hemorrhage control
II. Debridement
III. Hollow viscus disturbances
A. Ileus
B. Access for feeding
C. Fistula formation

Table 5.10 Risks for Intestinal Fistula Formation

I. Open abdomen
II. Intestinal injury
A. Trauma
B. Disease
C. Iatrogenic
III. Open abdomen management

Table 5.11 Management of Enteric Fistula

I. Sepsis control
A. Identification of a collection
B. Drainage
C. Systemic antibiotics for cellulites
II. Nutrition
A. TPN – most practical
B. Enteral – may be preferred but more difficult to provide
III. Local wound care
A. Floating stoma
B. V.A.C. sponge stoma

Abbreviations: TPN, total parenteral nutrition; V.A.C.,vacuum assisted closure.

necrotic tissue can follow trauma (e.g., liver, pancreas), infection (infected pancreatic necrosis), and ischemia (small bowel infarction).

Hollow viscus disturbances can prove to be the most challenging (Table 5.10). Protection of the bowel from injury, repair of the bowel when injured, use of the intestine for feeding, and management of intestinal fistula formation can all tax surgical technique and decision making.

Protection of the bowel with living tissue is preferred. Patients who achieve primary fascial closure within a few days are less likely to develop bowel injury. The omentum can protect the bowel, and it is preferred to cover an anastomosis with omentum or place an anastomosis under the cover of other living tissue (bowel, parietal peritoneum) rather than leaving a closure site visible in the open wound. In case of an injured bowel, the type of bowel closure does not influence the healing rate.

The use of decompressive tubing in the lumen of the intestine is controversial and can be technically challenging in the setting of the open abdomen, as can be gaining access for intestinal feeding. While some data support the use of early intestinal feeding for the open abdomen, it is difficult to separate degrees of intestinal malfunction and severity of insult in retrospective analysis. However, early feeding does not appear to be injurious, and it is usually feasible to initiate gastric or duodenal feeding before "closure" is obtained (31).

The critical surgical abdomen is the principal risk for an intestinal fistula that is in communication with the open wound [termed an enteroatmospheric fistula (EAF)]. Clearly, bowel injury promotes fistula formation. The more controversial aspect is whether the technique used to manage the open abdomen influences fistula formation. Particular concern about the insertion of polypropylene mesh has been raised in a recent publication (27). The use of the

V.A.C. system (Kinetic Concepts, Inc. San Antonio, TX) has also been questioned. In comparison, data regarding the use of the Wittmann patch seem favorable (31).

The principles of management of an enteric fistula are listed in Table 5.11. While these may be practical and sufficient when a fistula communicates to the skin (enterocutaneous fistula), it is unlikely that an EFA will close spontaneously. Therefore, much of the technical aspects of management are directed at controlling the EFA output in order to minimize or eliminate the continuing contamination of the open wound. The use of materials that cover the viscera to create an artificial stoma ("floating stoma," V.A.C. sponge configuration) can be effective and eventually allow skin grafting of the wound granulation tissue that covers the non-fistula viscera (31,32). Most often the fistula is taken down months later when the skin graft is separable from the abdominal viscera and can be combined with abdominal wall reconstruction (27).

SUMMARY

Damage control resuscitation, damage control laparotomy, and management of the abdominal compartment syndrome are the principal components of the critical surgical abdomen. The critical care surgeon provides the leadership for management of the critical surgical abdomen that non-surgical providers cannot offer. Besides technical expertise, the critical care surgeon must utilize knowledge and decision-making skills that emphasize an understanding of shock, massive transfusion, circulatory pathophysiology, and multiple organ failure. This knowledge and decision making can be implemented in the field, at a transferring facility, trauma bay, operating room, as well as intensive care unit.

Thus, the critical surgical abdomen serves as a paradigm for bringing the expertise of the critical care surgeon to the minute by minute, hour by hour, and day by day management of critical surgical illness.

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6 | The pulmonary system

PHYSIOLOGY AND PATHOPHYSIOLOGY

The lung primarily accomplishes two life-sustaining processes: addition of oxygen to and removal of carbon dioxide from the blood (gas exchange). Approximately 300 million alveolar-capillary units with ventilation (V) and perfusion (Q) accomplish this task. This section describes the various relationships of V to Q, the mechanics of respiration, and fluid movement in the lung.

LUNG VOLUMES

Figure 6.1 is a graphic representation of lung volume components that are meaningful for both negative pressure and positive pressure respiration (1). Tidal volume (VT) is the most frequent volume of air moved into and out of the lungs. Functional residual capacity (FRC), the amount of volume remaining in the lung after a normal expiration, is particularly relevant to upcoming discussions of respiratory failure and ventilator management. Critical closing volume (CCV, not shown in Fig. 6.1) is the lung volume at which small airways collapse, resulting in microatelectasis. Normally, CCV is less than FRC. However, with increasing age, chronic lung disease, and acute lung disease, CCV may become larger than FRC, resulting in significant atelectasis and an increase in physiologic shunt fraction (2).

Dead Space and Alveolar Ventilation

Dead space (VD) is the amount of VT (usually about 30%) that does not come in contact with pulmonary blood and cannot aid gas exchange. VD has two components: (1) anatomic—nose, mouth, trachea, bronchi, bronchioles; (2) physiologic—areas of lung parenchyma that are well ventilated but poorly perfused (i.e., V/Q approaches infinity) (Fig. 6.2). Alveolar ventilation (VA), the ventilation of perfused alveoli, is the difference between tidal volume (VT) and VD (3).

$$VA = VT - VD$$

Determinants of Arterial PCO_2 and PO_2

The determinants of arterial PCO_2 and PO_2 ($PaCO_2$, PaO_2) are listed in Table 6.1. PCO_2 is directly proportional to the ratio of dead space to tidal volume, VD/VT. As VD ventilation approaches VT, carbon dioxide cannot be eliminated (VD/VT = 1). Methods used to reduce an elevated PCO_2 include reduction of VD (i.e., tracheostomy to replace an endotracheal tube) or an increase in VT (i.e., relief of bronchospasm). Increasing rate of respiration to lower PCO_2 will be successful only if there are areas of lung having a low VD/VT ratio. If the entire lung has a high VD/VT ratio, simply increasing respiratory rate will be ineffective (3).

The carboxyhemoglobin dissociation curve is steep and almost linear, as compared to the oxyhemoglobin dissociation curve (Fig. 6.3). Increasing oxygen saturation reduces affinity and facilitates CO_2 release in the lungs; lower oxygen saturation increases affinity and augments CO_2 removal from the tissues. The nature of this curve allows a well ventilated and perfused area of lung to markedly reduce CO_2 content and compensate for lung areas not engaged in gas exchange (1).

Carbon dioxide is the end product of the metabolism of carbohydrate, protein, and fat. Increased metabolic demands (e.g., exercise, infection) increase O_2 use and CO_2 production. The ratio of CO_2 production to O_2 use is respiratory quotient (RQ), which is 1.0 for carbohydrate and protein and 0.7 for fat. Hypermetabolic states that use primarily carbohydrate and protein (e.g., severe inflammation) result in more CO_2 production than states that use primarily fat (starvation without inflammation).

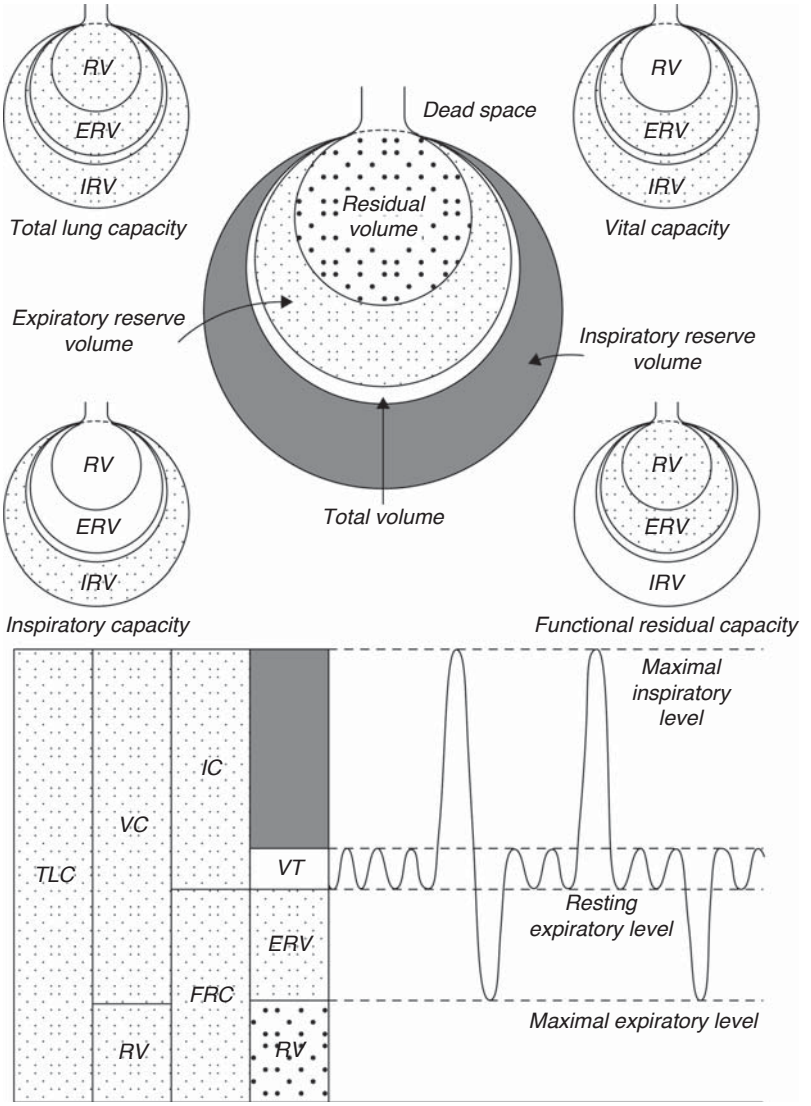

Figure 6.1 A schematic and spirographic representation of static lung volumes important to pulmonary physiology. *Abbreviations*: RV, residual volume; ERV, expiratory reserve volume; IRV, inspiratory reserve volume; TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; VT, tidal volume. *Source*: From Ref. 1.

The alveolar gas equation determines alveolar PO_2 (P_AO_2) and, therefore, the highest possible PaO_2.

$$P_AO_2 = (FiO_2 \times (P_{atmos} - P_{H2O})) - (P_ACO_2 \times [FiO_2 + (1 - FiO_2)/RQ]$$

Where, FiO_2 is the fraction of oxygen in inspired air, P_{atmos} is the atmospheric pressure (760 mm Hg at sea level), P_{H2O} is the partial pressure of water in the alveolus (47 mm Hg at 37°C), P_ACO_2 is mean alveolar PCO_2 (usually close to arterial PCO_2) (1).

Increasing body temperature and the resultant increase in P_{H2O} as well as elevated P_ACO_2 can both lower PaO_2, but the effect will be less as FiO_2 increases. The alveolar gas equation is the clearest demonstration of the interaction between oxygen being added to the blood and CO_2 being eliminated. Otherwise, the two processes are best thought of as separate.

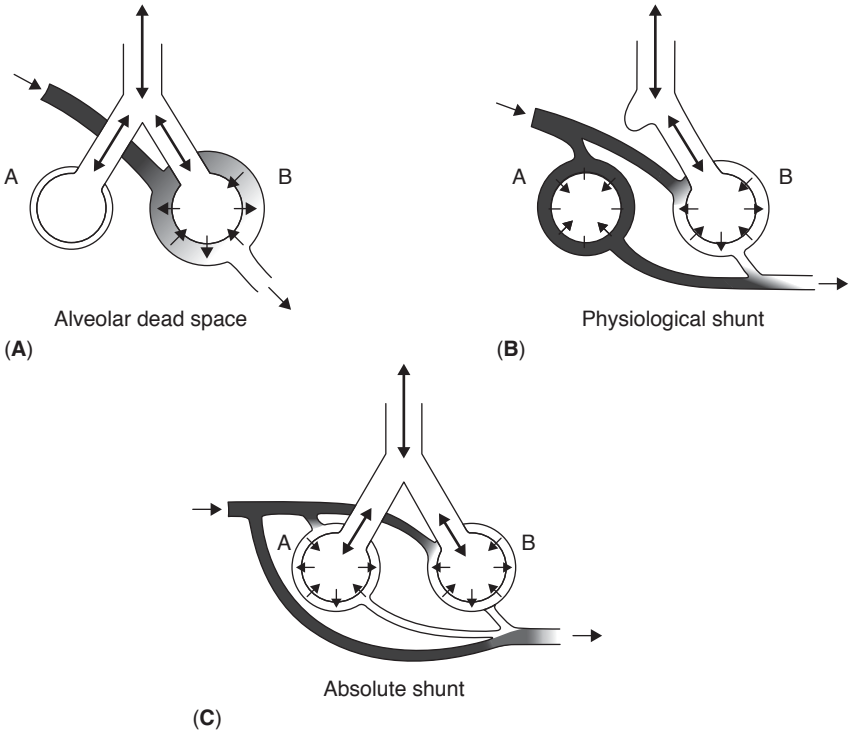

Figure 6.2 Panel (**A**) is a schematic representation of lung units with ventilation and no perfusion (alveolar dead space). There is uniform ventilation to A and B, with no blood flow to A. Panel (**B**) represents lung units with perfusion to A and B, but no ventilation to A (physiological shunt). Panel (**C**) represents lung units with uniform ventilation and blood flow to A and B, but there is venous blood that bypasses alveoli (anatomical shunt). *Source*: From Ref. 1.

Table 6.1 Determinants of $PaCO_2$ and PaO_2

I. $PaCO_2$
• Ratio of dead space to tidal volume VD/VT
• Anatomic dead space
• Physiologic dead space
• Carboxyhemoglobin dissociation curve
• CO_2 production
II. PaO_2
• Alveolar gas equation
• FIO_2
• PCO_2
• Ventilation – perfusion inequality
• Shunt
• Decreased cardiac output
• Diminished diffusion capacity

Ideally, the ventilation and perfusion of alveoli are perfectly matched (V/Q = 1). Areas that are ventilated but not perfused (V/Q = infinity) are physiologic VD units; areas that are perfused but not ventilated (V/Q = 0) are physiologic shunts. A shunt (Qs) represents venous blood that does not come in contact with ventilated alveoli (Fig. 6.2, middle and bottom). Similar to VD, there is a normal anatomic component of shunting [5–6% of cardiac output (Qt)] that consists principally of the blood supply to the bronchioles and heart, which then drains directly

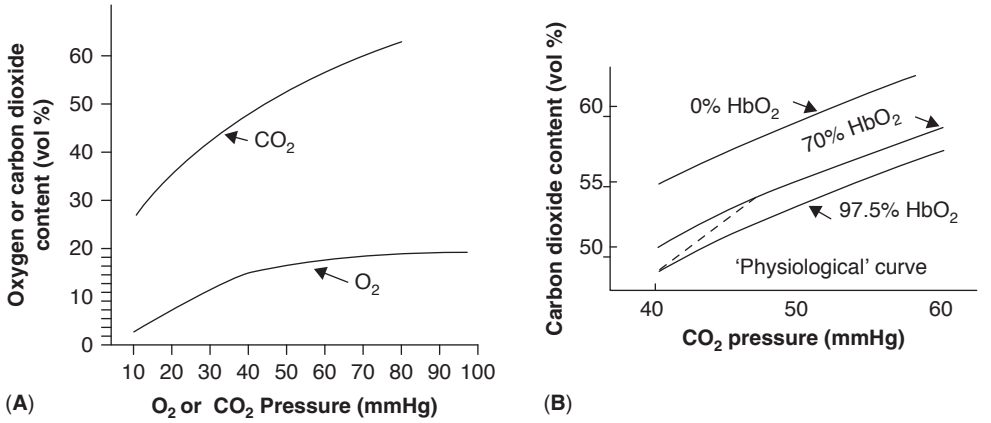

Figure 6.3 Carbon dioxide dissociation curves illustrating (**A**) the almost linear relationship between the pressure of carbon dioxide and the content, and (**B**) increasing oxygen saturation reducing affinity and facilitating CO_2 release in the lungs. *Source*: From Ref. 1.

into the pulmonary veins or the left ventricle, respectively. Areas of lung that simulate VD will affect PaO_2 via the alveolar gas equation. Areas that simulate a shunt will diminish PaO_2 by the admixture of venous blood with newly oxygenated blood.

With minimal shunting, mixed venous oxygen content will have little effect on PaO_2. Increasing the shunt increases this influence. Under these circumstances, variables that decrease mixed venous oxygen saturation (decreased cardiac output, increased oxygen utilization) can significantly diminish PaO_2 and may lead to therapy directed at improving lung function (4). Similarly, increasing cardiac output may improve PaO_2 and lead to a false interpretation that the lung is better. Measurement of cardiac output and calculation of the shunt percentage as well as oxygen delivery and consumption, can help sort out the influence of cardiac output and oxygen consumption on arterial oxygen concentration.

Shunt equation (percent of cardiac output engaged in the shunt effect):

$$Qs/Qt = [(P_AO_2 - PaO_2) \times 0.0031]/[(CaO_2 - CvO_2) + (P_AO_2 - PaO_2) \times 0.0031]$$

where CaO_2 is arterial oxygen content and CvO_2 is mixed venous oxygen content (3).

$$\text{Oxygen content} = 1.34 \times \text{hemoglobin (g/dL)} \times \text{oxygen saturation} + 0.0031 \times PO_2$$

The average V/Q relationship of a normal lung is close to unity, but gravity is a determinant of the relative ratio of ventilation to perfusion in different areas of the lung. For instance, pulmonary blood flow is several times greater at the bases as compared to the apex in an upright man (5). Proportionally, however, ventilation is greatest at the apex. West has divided the lung into three zones that describe the ratio of intra-alveolar pressure (PAV) to pulmonary arterial (PA) and venous (PV) pressure: Zone I, PAV > PA > PV; Zone II, PA > PAV > PV; Zone III, PA > PV > PAV (Fig. 6.4) (6). Pulmonary artery occlusion pressure equals pulmonary venous pressure and, therefore, measures left atrial pressure most reliably in Zone III, where the catheter tip is vertically below the left atrium. Fortunately, since the catheter is flow directed, most often the tip does locate in Zone III.

More recent investigation has demonstrated that this vertical, gravity-dependent influence on ventilation and perfusion is accompanied by equal, if not greater, differences in the horizontal (isogravitational) planes of the lung. It is possible for high-perfusion regions to persist regardless of posture and blood flow is greater in the central regions of the lung as compared to the periphery. Similar findings have been noted with ventilation (5).

Diminished diffusion capacity is generally of little clinical significance in surgical critical care and likely to cause hypoxemia only when FiO_2 is low (high altitude), with thickened alveolar capillary membranes (interstitial fibrosis), or with shortened exchange time (very high cardiac output).

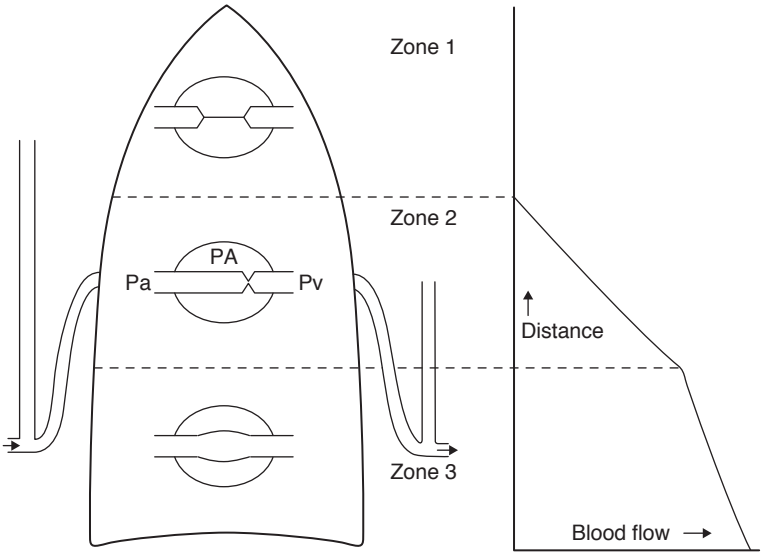

Figure 6.4 Schematic illustration of the relationship between alveolar pressure (PA), pulmonary arterial pressure (Pa), and pulmonary venous pressure (Pv) in different zones of the lung. In zone 1, PA is greater than both Pa and Pv. In zone 2, Pa is greater then PA and Pv. In zone 3, Pa is greater than Pv, which is greater than PA. *Source*: From Ref. 6.

Table 6.2 Major Components of Pulmonary Mechanics

- Inspiratory pressure
- Expiratory pressure
- Compliance/elastance
- Resistance
- Airway pressures
- Work of breathing

Pulmonary Mechanics

The mechanics of respiration (Table 6.2) are important determinants of the need for respirator support. The following text and accompanying tables provide a brief description of the fundamentals that can be applied commonly in clinical practice.

Muscles of Respiration

The diaphragm is the major muscle of respiration. During quiet respiration, the costal and crural fibers that insert on the central tendon push the abdominal viscera down and produce negative intrathoracic pressure. The intercostal muscles are much less important, unless diaphragmatic weakness or paralysis is present, in which case there is inward displacement of the abdominal wall during inspiration. Other muscles assisting inspiration are the scalene and the sternocleidomastoid. Maximal contraction of inspiratory muscles can generate a negative intrapleural pressure of 60–100 mm Hg (1).

Expiration is usually passive. Active expiration incorporates all the muscles of respiration, with the abdominal muscles most important. Pressures up to positive 119 mm Hg have been documented (1).

Compliance/Elastance

Expansion of a lung can be likened to the expansion of a balloon. In a comparison of two balloons subjected to the same increment in transmural pressure, if balloon 1 expands to a larger

Table 6.3 Formulae for Pulmonary Mechanics

- Compliance (C) = $\Delta V/\Delta P$
- Total Compliance (CT): 1/CT = 1/CCW + 1/CL
  where CCW = chest wall compliance, and CL = lung compliance.
- Resistance (R) = $\dfrac{\text{Pressure Beginning (PB)} - \text{Pressure End (PE)}}{\text{Flow Rate}}$
- Airway Resistance (RAW) = $\dfrac{\text{PM} - \text{PALV}}{\text{Flow Rate}}$
  where, PM = pressure at mouth, PALV = alveolar pressure and resistance is described in units cm H_2O/L/sec (normal 2–3 in the spontaneously breathing adult).
- Pressure drop during laminar flow:
  $PB\text{-}PE = K1 \times L \times 1/r^4$
  where, K1 = constant related to flow rate and viscosity, L = length of tube, and r = radius of the tube.
- Pressure drop during turbulent flow:
  $PB\text{-}PE = K2 \times (\text{flow rate})^2$
  where K2 = constant related to length and radius of tube along with viscosity and density of the gas.

volume than balloon 2, then balloon 1 has more compliance but less elastance. Compliance is the ratio of the change in pressure to the change in volume. Elastance is the opposite of compliance and represents the intrinsic elastic component that resists deformation by stress. The relationship between transmural inspiratory and expiratory pressures and lung volumes is determined by the compliance of the chest wall and lungs (total compliance, Table 6.3). Without disease, total compliance (CT) is determined mostly by the elastic recoil properties of the lung (CL) and thorax (CW). With negative pressure, the inspiration CT equals approximately 0.1 L/cm H_2O. Under conditions of mechanical ventilation CT in patients with normal lungs and chest walls, CT is approximately 0.05 L/cm H_2O. Certain diseases (e.g., circumferential thoracic burns) diminish primarily chest wall compliance, while others (e.g., pulmonary edema) diminish primarily lung compliance. Critically ill patients commonly develop alterations in both components of total compliance.

The compliance described above is measured as a given inflation volume is held constant (static compliance). The relationship between volume and pressure can be plotted (pressure-volume curve, P-V curve, Fig. 6.5) and the slope of this curve represents compliance. As seen in the figure, a normal lung exhibits a similar relationship between pressure and volume as pressure is gradually increased and then decreased (left part of the figure). With certain diseases [acute respiratory distress syndrome (ARDS) in this case, right part of the figure], the pressure volume curve exhibits significant hysteresis, indicating that compliance changes as lung volume units open when pressure is increased and then close as pressure is decreased. The changes in static compliance with different inflation volumes can be plotted (Fig. 6.6) to produce a characteristically sigmoidal curve. An increase in compliance is greatest in the mid-volume range (where VTs usually occur) and is the least at total lung capacity (top right of the curve) and low lung volumes (bottom left of the curve) near FRC or RV.

Resistance

Any fluid (air is considered a fluid) moving through a tube meets resistance to flow. Because of this resistance the pressure measured at the end of the tube will be less than the pressure measured at the beginning of the tube. This difference in pressure is related to both the resistance and the flow rate of the fluid (Table 6.3). Flow in tubes can be described as linear and turbulent. Variables that influence the pressure drop (and thereby resistance) across a tube during linear flow are the viscosity of the fluid and the length and radius of the tube. The influence of radius on resistance during laminar flow is profound. With a sufficient increase in flow rate in a tube (the critical flow rate), turbulent flow develops. With turbulent flow, all variables that influence the pressure drop during linear flow are in effect but, in addition, the density of the gas and square of the flow rate are important variables (Table 6.3) (1).

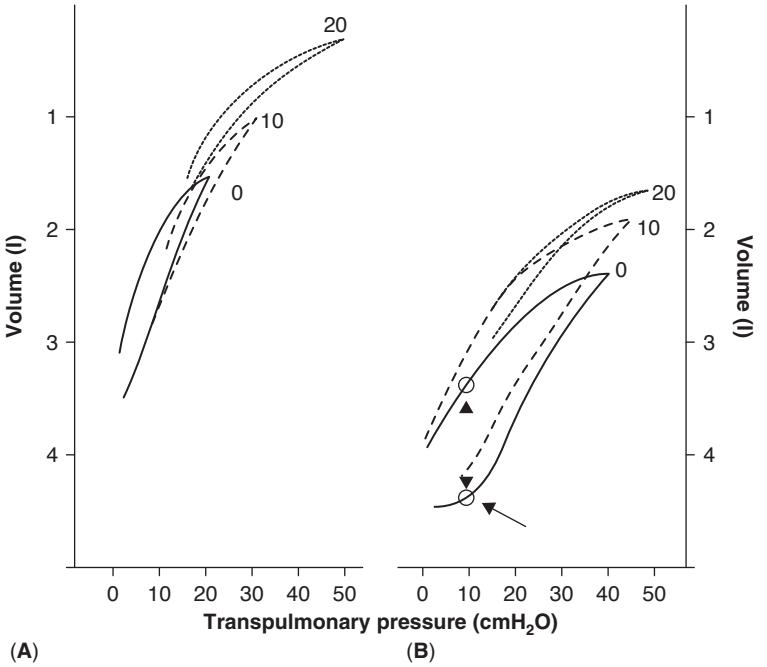

Figure 6.5 Static pressure-volume curve as an indication of compliance. The slope of the curve represents compliance. (**A**) Shows compliance of a normal lung, and (**B**) shows the compliance of a lung from a patient with acute respiratory distress syndrome. Both a and b show the change or lack of change in compliance with the addition of positive end-expiratory pressure (PEEP). The diseased lung (**B**) exhibits a more normal volume-pressure relationship following the application of PEEP. *Source*: Marcy TW, Marcini JJ. Inverse ratio ventilation in ARDS: rationale and implementation. Chest 1991; 100:494–504.

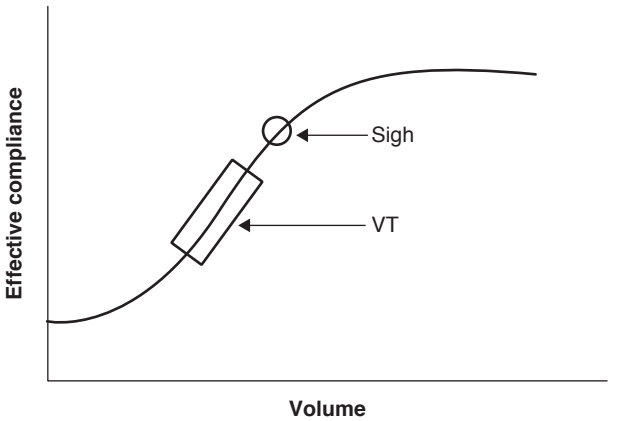

Figure 6.6 Effective compliance versus lung volume. Compliance is greatest in the mid-volume range, where tidal volumes (VT) usually occur. The increase in volume of a sigh normally remains in the range where compliance can still increase. *Source*: Rochon RB, Mozingo DW, Weigelt JA. New modes of mechanical ventilation. Surg Clinics N Am 1991; 71:843–57.

Airway Pressures

During negative pressure ventilation, the lung is subjected to little potential damage from pressure effects. Positive pressure ventilation, however, results in several airway pressure alterations that may yield beneficial effects (improved oxygenation and carbon dioxide removal) and detrimental effects (decreased cardiac output and lung damage). The airway

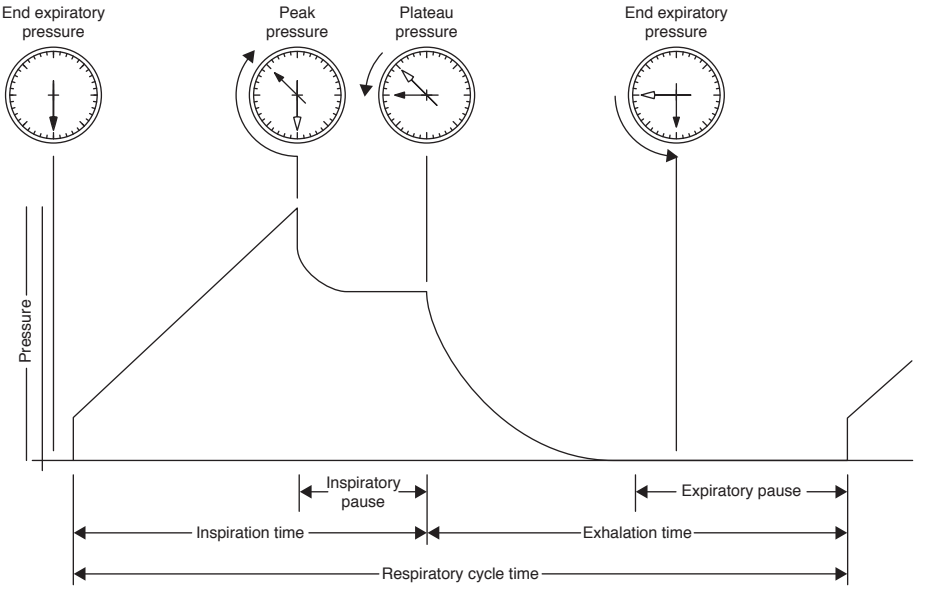

Figure 6.7 Pressures of the respiratory cycle during controlled mechanical ventilation. *Source*: Depuis YG. Ventilators: Theory and Clinical Application. St. Louis: Mosby Year Book, 1992.

pressures that have received the most attention in surgical critical care are as follows: mean airway pressure ($\overline{P}$aw), peak inspiratory pressure (PIP), the pressure at end inspiration (plateau pressure, Pplat), alveolar pressure (Palv), transpleural pressure (Ptrans), and positive pressure at the end of expiration (PEEP).

$\overline{P}$aw is the mean pressure monitored in the airway during the entire respiratory cycle. $\overline{P}$aw is influenced by mean alveolar pressure, but is not a direct measurement, being influenced by such variables as inspiratory resistance as well as the inspiratory/expiratory time cycle. Despite this, $\overline{P}$aw is a variable that can be linked to the oxygenation and cardiovascular effects of positive pressure mechanical ventilation. On average, as $\overline{P}$aw increases, oxygenation improves and venous return decreases (7).

PIP is the maximum pressure generated in the airway during gas flow (Fig. 6.7). PIP can be influenced by compliance, airway resistance, VT, and the rate of flow of gas. Pplat is the pressure in the airway at the end of inspiration during a positive pressure VT, but before exhalation begins (inspiratory pause). Pplat (Fig. 6.7) is a measure of peak alveolar pressure. During the inspiratory pause, there is a drop from PIP as gas distributes from the upper to the lower airways. Pplat is mostly affected by total thoracic compliance (8).

Palv is the pressure in the alveolus during the entire respiratory cycle. Palv is closely approximated by $\overline{P}$aw in many clinical circumstances, especially when inspiratory and expiratory resistances are nearly equal and airway flow rates are low. At zero flow, $\overline{P}$aw does equal Palv. However, during flow and especially when expiratory resistance is higher than inspiratory resistance, $\overline{P}$aw will underestimate Palv, especially when minute ventilation is high. That is, when air meets more resistance leaving the alveolus than when air is brought to the alveolus, alveolar pressure will increase in proportion to the amount of air brought to the alveolus each minute (9).

The change of Palv during the respiratory cycle has a direct influence on pleural pressure (Ppl), which is also influenced by the compliance of the lung (CL) and chest wall (CW) (7).

$$\Delta \text{Ppl} = \Delta \text{Palv} \times (\text{CL}/(\text{CL} + \text{CW}))$$

Ppl is inversely related to alterations in venous return. That is, an increase in Ppl will result in a decrease in venous return. Therefore, an increase in Palv in compliant lungs will

have a more significant effect on Ppl and venous return than an increase in Palv in non-compliant lungs (7). On the other hand, non-compliant lungs will develop less of an increase in pleural pressure and more of an increase in transpulmonary pressure (Ptrans) as Palv increases.

Ptrans is the pressure difference between the alveolus and the pleural space, as described by the following formula:

$$\text{Ptrans} = \text{Palv} - \text{Ppl}$$

As discussed in the section on "Ventilator-Induced Lung Injury," Ptrans is an important feature of the risk of ventilator-induced lung injury (VILI) (10).

PEEP is pressure present in the airway at the end of expiration. PEEP is often applied to the ventilator circuit as part of ventilator management (external PEEP). In addition, disease states that result in a failure to return to passive FRC before the onset of the next inspiration (high expiratory resistance – dynamic hyperinflation), and ventilator settings that result in a similar phenomenon (increased inspiratory time to expiratory time ratio – I:E ratio) can result in increased alveolar pressure at the end of expiration (auto-PEEP). For patients on a ventilator, auto-PEEP may be present whenever the flow tracing shows flow at the end of exhalation. Total PEEP is the sum of externally applied PEEP and auto-PEEP. Measurement of end-expiratory occlusion pressure (the airway pressure at end-expiration with the expiratory port occluded) provides total PEEP. The difference between this and externally applied PEEP is auto-PEEP. Auto-PEEP can increase $\overline{P}aw$ and Palv in the same fashion as external PEEP and, therefore, has the same potential to influence hemodynamics and transalveolar pressure (8).

Work of Breathing

The work of breathing is performed to overcome airway resistance and the recoil of the lungs and chest wall (Table 6.4). Change in volume multiplied by the pressure difference forcing the change in volume equals work (1).

The work performed to stretch the lungs and chest wall becomes potential energy for expiratory work. Since the airway narrows during expiration, resistance increases, but normally not enough to inhibit expiration. With increasing resistance (i.e., bronchospasm), more work must be performed during expiration to raise the intrathoracic pressure above atmospheric pressure, which in turn compresses the airway.

The work of breathing may be measured in mechanical units or by oxygen consumed by the respiratory apparatus. Normally, the respiratory muscles consume <5% of total body oxygen. As expected, with increasing work, respiratory muscle oxygen demand increases (1).

Pulmonary Fluid

The physiology of the movement of intravascular fluid and protein into and out of the pulmonary interstitium has been well studied and is described by Starling's equation:

$$Jv = Lp \times A \times [(Pc - Pt) - \sigma(\pi c - \pi t)]$$

Where Jv is the magnitude of fluid migration per unit of time; Lp is hydraulic conductance or the speed at which fluid can pass through the microvascular exchange barrier; A is the

Table 6.4 Work of Breathing Variables

- Airway resistance
- Lung and chest wall compliance
- O_2 consumption and production
- V/Q coordination
- Hyperventilation

surface area available for exchange; σ is the reflection coefficient, or the relative permeability of the microvascular membrane to plasma proteins; Pc is the plasma hydrostatic pressure; Pt is the interstitial hydrostatic pressure; πc is the plasma colloid oncotic pressure; πt is the interstitial colloid oncotic pressure (11,12).

In the lung, as in other organs, the migration of fluid and protein, especially albumin, into the interstitial space is normal at the high pressure end of capillaries, is partially returned to the circulation as the hydrostatic pressure falls, but also returns to the circulation via the lymphatics. Interstitial and subsequent alveolar edema does not occur until the lymphatics are overwhelmed. Pulmonary lymphatics may be capable of removing several times the usual amount of interstitial fluid before edema develops. Pulmonary lymphatics appear to be more capable of this function than those that drain the systemic circulation (13–15).

Starling's equation and the physiology of lymphatic drainage allow for several etiologies of pulmonary edema (Table 6.5) (12). The "true" hydrostatic pressure in the pulmonary capillary (Pcap) is determined by mean PA pressure and LAP or PAOP, as well as pulmonary arterial and venous resistance (see chap. 3) (16). While normal conditions allow an estimate of Pcap from a published formula, disease alters the listed variables sufficiently to preclude accuracy (Table 6.6). Measurement of Pcap is possible using the pulmonary artery tracing available through a pulmonary artery catheter. Disease will usually result in an increase in Pcap compared to PAOP (16), but the increase is not typically large, (i.e., <5 mm Hg).

The most common etiology of an increase in Pc is left heart failure. When Pc is elevated, a good correlation between radiographic indices of increased lung water and hydrostatic pressure has been documented (Table 6.7). In addition, an increase in hydrostatic pressure (typically >20 mm Hg) can result in increased extravascular lung water (EVLW) that correlates well with deficits in oxygenation (Fig. 6.8) (16–18).

Table 6.5 Possible Etiologies of Pulmonary Edema

- Increased pulmonary microvascular pressure
- Decreased oncotic pressure
- Increased capillary permeability
- Obstructed lymphatics

Table 6.6 Common Etiologies of Pulmonary Arteriolar Constriction

- Hypoxia
- Hypercapnia
- Bronchospasm
- Pulmonary edema (any etiology)
- Severe inflammation
- Pulmonary embolism

Table 6.7 Radiographic Correlation Hydrostatic Pressure Increase in Normal Lungs

PCW	Radiographic Finding
<16–18	Normal
18–22	Cephalization
22–25	Perihilar haze
25–30	Periacinar rosette
>30	Dense alveolar infiltrates

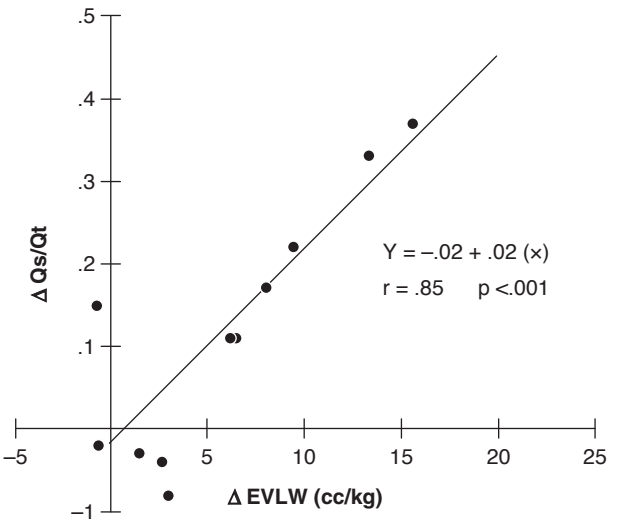

Figure 6.8 The correlation between the change in extravascular lung water (EVLW) and the corresponding change in physiologic shunt (Qs/Qt). *Source*: From Ref. 17.

More controversial is the effect of low plasma oncotic pressure (πc) with normal hydrostatic pressure and normal pulmonary capillary permeability. Experimental data are conflicting, but human data do not support this as a principal etiology of lung water accumulation (12,15,16,19,20).

An increase in pulmonary capillary permeability as a mechanism of interstitial and alveolar fluid accumulation has been extensively investigated in both experimental and human models. In contrast to an increase in Pc, an increase in permeability (σ) does not result in a good correlation between EVLW and either radiographic or oxygenation alterations (Fig. 6.9) (21–29). As further discussed in the section "Effects of Systemic Inflammation on the Lung" EVLW contributes, but does not completely explain the pathophysiological alterations characteristic of permeability pulmonary edema. Therefore, management strategies differ from that employed when hydrostatic edema is the principal alteration.

The most common diseases obstructing lymphatics are malignancies that either invade the mediastinal lymphatics (lymphoma, metastatic lung cancer) or spread in the interstitium of the lung (breast cancer, leukemia). This form of pulmonary edema is usually unresponsive to common treatment but may improve if the malignancy is treated.

Pulmonary Monitoring

History and Physical Examination

Pulmonary monitoring begins with history and physical examination. History should provide information regarding severity of dyspnea, cough, sputum production, smoking, bronchospasm, previous lung infections, and previous thoracic surgery. On physical examination, observation is the first and often only maneuver required for the diagnosis of mild, moderate, or severe respiratory distress. Skin color (cyanosis), mental status (anxiety, agitation), respiratory rate, depth, symmetry, and pattern of respiratory muscle use provide clues relevant to the work of breathing and gross gas exchange inadequacies (e.g., lack of motion of a hemithorax, marked tachypnea, shallow respiration, flail chest, and use of accessory muscles). Palpation can discover crepitus and augment the recognition of asymmetrical size or movement. Auscultation helps determine the presence or absence of air movement, and can provide evidence of

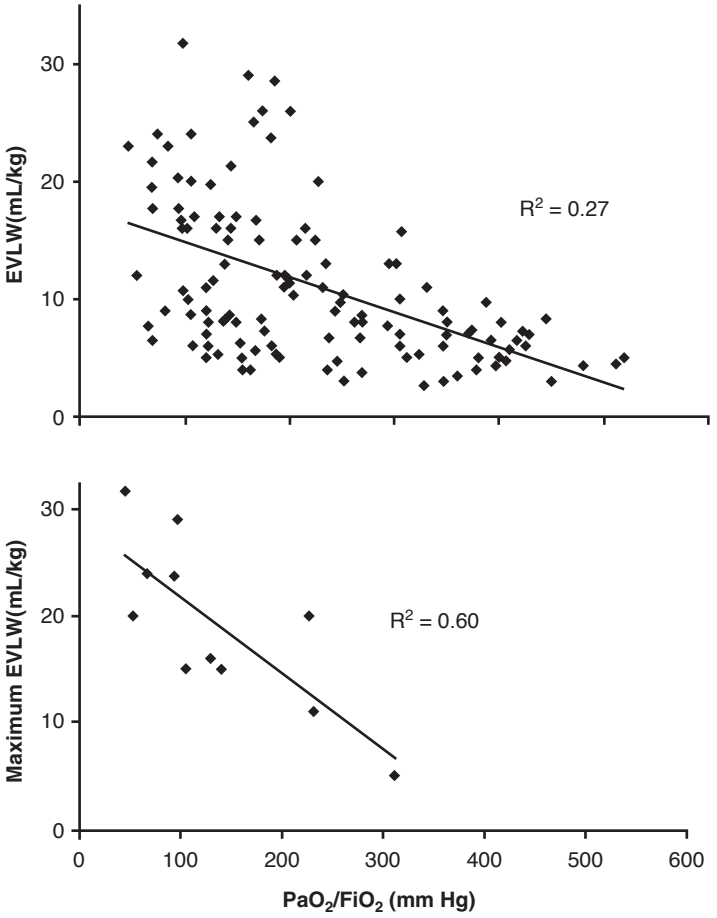

Figure 6.9 Scatter plot showing the relationship between extravascular lung water (EVLW) and pO_2/FiO_2 in patients with severe sepsis. Despite the statistical relationship, there is a very poor correlation coefficient for all data, which improves for maximum EVLW effect, yet cannot account for 40% of the variance. *Source*: From Ref. 22.

increased lung water, consolidation, and bronchospasm. Percussion helps delineate the presence of excess air (tympany) or excess fluid (dullness).

Observation alone is often sufficient to diagnose respiratory distress worthy of mechanical support. That is, the diagnosis of respiratory failure can be a clinical, bedside diagnosis, rather than dependent upon the laboratory information discussed below.

Chest Radiography

Plain chest radiography and computed tomography (CT) of the chest are important adjuncts to history and physical examination findings. Chest CT without intravenous contrast is more sensitive for pulmonary parenchymal and pleural alterations and is particularly useful when the plain chest radiograph is unrevealing. In addition, the patterns of parenchymal changes are better delineated by chest CT that may have important diagnostic implications (see section "Effects of Systemic Inflammation on the Lung"). Chest CT with intravenous contrast is used primarily for the diagnosis of pulmonary embolism (see below).

Table 6.8 PaO_2/FiO_2 Compared to SPO_2/FiO_2

Sofa Respiratory Score	P Ratio	S Ratio
1	<400	<512
2	<300	<357
3	<200	<214
4	<100	<89

Arterial Blood Gases and Saturation

The determinants of arterial blood gas (ABG) measurements are described above. ABG data are useful for both the evaluation and management of pulmonary alterations. While calculation of the physiologic shunt is a precise clinical measure of pulmonary function, the necessity of pulmonary artery catheter placement makes this monitor impractical for most clinical evaluations and investigations. In addition, calculation of alveolar PO_2 (see alveolar air equation) allows measurement of the difference between alveolar oxygen and arterial oxygen (A-a gradient). The complexity of this calculation makes the use of this parameter unattractive. Instead, the ratio of PaO_2 to inspired oxygen concentration (FiO_2) has supplanted the calculated shunt and A-a gradient as monitors of pulmonary oxygenation. The normal ratio is ≈500, and values <200 are indicative of severe oxygenation alterations. As described above, when physiologic shunt is increased, PaO_2 is influenced by mixed venous oxygen saturation, a feature accounted for by the shunt equation, but not by the PaO_2/FiO_2.

Constant arterial oxygen saturation monitoring (SPO_2) is commonplace for hospitalized patients and patients undergoing procedures. The principal confounder for saturation monitoring is the perfusion at the site that the monitor is placed, such that more "central" locations, that is, ear lobe, may be necessary when peripheral perfusion, that is, to the digits, is compromised (30). In the critical care setting, SPO_2 has been found to be sufficiently reliable for replacing PaO_2 in order to calculate the oxygenation ratio. For instance, SPO_2/FiO_2 <214 is the equivalent of PaO_2/FiO_2 <200 (Table 6.8) (31).

Sometimes, the magnitude of gas exchange threat is not evident by clinical evaluation and the ABG and/or arterial saturation data prompt the diagnosis of respiratory failure and the need for mechanical support. However, sometimes the ABG data are not persuasive ("His gases were good.") and delay intervention despite obvious distress at bedside evaluation. Under these circumstances, the clinician should be expecting a rapid response to therapy, that is, relief of bronchospasm, expansion of a pneumothorax, etc. If the etiology of distress and/or the onset of improvement are uncertain, it is better to provide mechanical support for clinical respiratory distress despite the "good" arterial blood gases or saturation.

LUNG DYSFUNCTION

Surgical patients can suffer many threats to pulmonary function (Table 6.9). These threats can be cataloged into alterations that principally disturb chest wall mechanics (mechanical threats) and those that disturb alveolar gas exchange directly (alveolar threats). The alterations that are most problematic during surgical critical illness are emphasized in this section.

Effect of Hypoperfusion on the Lung

The main effect of hypoperfusion either to the entire lung or regions of the lung is an increase in physiologic VD. During systemic hypoperfusion, little alteration in oxygenation occurs. Once hypoperfusion has been reversed, the effect of the initiating insult (hemorrhage, abdominal sepsis) can become manifest, depending on the degree of the resultant systemic inflammation.

Effects of Systemic Inflammation on the Lung (Indirect ALI and Indirect ARDS)

Decreased alveolar lung function is characteristic of severe systemic inflammation. A marked increase in physiologic shunting and physiologic VD as well as a variable increase

Table 6.9 Etiologies of Diminished Lung Function During Surgical Critical Illness

1. Atelectasis
   - Secretions
   - Hypoventilation
   - Airway obstruction
2. Hypoventilation
   - Anesthesia
   - Narcotics
   - Supine position
   - Splinting-thoracic > upper abdominal > lower abdominal
   - Chest wall trauma
   - Obesity
3. Lung Injury
   - Direct—local inflammation
     Contusion
     Aspiration
     Inhalation
     Near Drowning
   - Indirect—systemic inflammation
     Abdominal sepsis
     Pancreatitis
     Ischemia/reperfusion
     Multiple trauma
     Fat embolism
     Transfusion
     Urinary sepsis
     Extremity sepsis
     Cardiopulmonary bypass
4. Lung Infection—local inflammation
   - Community-acquired pneumonia
   - Nosocomial pneumonia
5. Thromboembolism

in EVLW frequently result in the institution of mechanical ventilation for the conditions most often designated as ALI and/or ARDS. In 1994, publications the American-European Consensus Conference (AECC) on ARDS provided definitions for ALI and ARDS, in keeping with the recognition of the spectrum of lung malfunction that can accompany these insults (Table 6.10) (32).

The etiologic mechanisms for ALI and ARDS were separated into direct and indirect (systemic) processes (Table 6.9), with lung infection included in the direct category. This separation has diagnostic, anatomic, and physiologic distinctions that can influence clinical activities such as the quest for a specific diagnosis; the administration of a specific therapy; the expected natural history. For instance, bilateral pulmonary contusions typically cause oxygenation deficits that begin to abate about 72 hours after injury. In contrast, the lung injury consequent to severe pancreatitis will usually parallel the severity and duration of the abdominal inflammation, features that are much less predictable.

The distinction of direct versus indirect lung injury has been shown to be associated with different lung pathology and physiology. For example, the "classic" pathological finding in ARDS is diffuse alveolar damage (DAD), but the magnitude and timing of DAD may be influenced by the injury pathway (33,34). In addition, physiologic alterations such as an increase in static elastance (reciprocal of compliance) may have different lung and chest wall components depending upon the injury mechanism (34).

The indirect (systemic) mechanisms of ALI and ARDS result in migration of inflammatory cells to the lung as well as cell activation and tissue sequestration that is associated with alterations in endothelial cells, platelets, and pneumocytes. Many inflammatory mediators

Table 6.10 AECC Definitions of Acute Lung Injury and Acute Respiratory Distress Syndrome

I. ALI
• Acute onset
• PaO_2/FiO_2 ≤300 mm Hg (regardless of PEEP)
• Bilateral infiltrates on chest radiograph
• PAOP ≤18 mm Hg when measured, or no clinical evidence of left atrial hypertension
II. ARDS
• Acute onset
• PaO_2/FiO_2 ≤200 mm Hg (regardless of PEEP)
• Bilateral infiltrates on chest radiograph
• PAOP ≤18 mm Hg when measured, or no clinical evidence of left atrial hypertension

Table 6.11 Systemic Mediators of Acute Lung Injury and Acute Respiratory Distress Syndrome

I. Cytokines
TNF-α
IL-1β
IL-6
IL-8
II. Innate immunity components
Complement activation
Platelet activation
PMN migration and sequestration
III. Reactive oxygen species
Ischemia/reperfusion
Generation at local inflammation sites

have been linked to this process, gaining access to the pulmonary circulation in an endocrine fashion from the site of mediator stimulation and release (Table 6.11) (27,35–38). Of note, while PMN sequestration and activation appear to be a common pathological feature of DAD, the pathology and physiology of ARDS can be seen in neutropenic patients who do not show PMN accumulation (39). Such findings infer a redundancy to inflammatory stimulation and activation that diminishes the probability that attention to one aspect of the inflammatory response (e.g., TNF α antagonism) will result in a desired outcome.

DAD proceeds through a temporal sequence: exudative phase (days 1–7), proliferative phase (days 7–21), and fibrotic phase (after day 21). Each of these phases may overlap with others, even within a lung region, and are not strictly limited to these time frames.

The exudative phase is characterized by interstitial and intra-alveolar edema, dense eosinophilic hyaline membranes, endothelial cell injury, and intracapillary aggregates of neutrophils. There is extensive necrosis of type 1 pneumocytes. The loss of alveolar epithelial barrier allows free escape of interstitial fluid into the alveolus. The pulmonary microvasculature can exhibit thrombi, either of embolic or in situ origin. Of note is the markedly different magnitude of pulmonary cellular alterations in ALI and ARDS as compared to hydrostatic edema formation (40).

The proliferative phase is associated with growth of type 2 pneumocytes, fibroblasts and myofibroblasts, and the formation of granulation tissue. This results in alveolar duct and alveolar space fibrosis.

The fibrotic phase is seen in patients who survive beyond three to four weeks, whereby the lung is remodeled by the deposition of collagen. This can also result in fibrous obliteration of the microcirculation and persistent pulmonary hypertension (33).

Patients who show little resolution of lung and systemic inflammation during the exudative phase demonstrate a poor prognosis for lung improvement (27). Presumably, then, management strategies directed at limiting the magnitude and duration of the exudative phase of

Table 6.12 The Differentiation of Acute Respiratory Distress Syndrome from Hydrostatic Edema

I. Clinical circumstances
A. Systemic inflammation
B. Known heart disease
II. Physical examination
III. Oxygenation impairment
IV. Chest CT
V. Invasive hemodynamic monitoring

ALI and ARDS can limit lung-related morbidity and mortality (see section on "Management of ALI and ARDS").

Diagnosis of ALI and ARDS

The potential etiologies of respiratory distress in surgical critical illness are numerous (Table 6.9). For surgical critical illness, the diagnostic evaluation for respiratory distress is incomplete if both direct and indirect ALI and ARDS are not included in the initial differential. While published diagnostic criteria for ALI and ARDS are important for clinical and experimental investigation, patients may not always meet these specifics at the onset of respiratory distress. Certainly, patients with direct causes of ALI and ARDS are more likely to exhibit early radiographic changes, but these may be delayed for patients with indirect injury. Therefore, it is important to consider indirect ALI and ARDS as a possibility, especially when the initial diagnostic steps (physical examination, chest x-ray, arterial blood gas data) are inconclusive.

When the diagnostic criteria are met, the most common diagnostic error is to misclassify the lung disturbance as secondary to hydrostatic pulmonary edema (the mechanism that accompanies congestive heart failure) and/or total body fluid sequestration (commonly termed "fluid overload"). Clinical and laboratory information that help distinguish a diagnosis are listed in Table 6.12.

First to evaluate is whether or not the patient has an illness and/or injury that would likely result in moderate to severe systemic inflammation. A patient six hours post operation following an emergency total colectomy for lower intestinal hemorrhage is more likely to circulate increased inflammatory mediators than someone six hours after an elective laparoscopic cholecystectomy (41,42). Similarly, a patient with severe pancreatitis is more likely to sequester several liters of fluid in the first 24–48 hours as compared to one with an isolated tibial fracture (43). The patient with moderate-to-severe systemic inflammation is more likely to be suffering indirect ALI or ARDS than from hydrostatic edema. Since EVLW accumulation is not the only cause of poor oxygenation in ARDS, invoking "fluid overload", as the primary mechanism does not fit known pathophysiologic mechanisms (see section on "Pulmonary Fluid").

"Fluid overload", as an etiology of pulmonary edema, should be confined to the concept of hydrostatic pulmonary edema (elevated pulmonary capillary pressures). This is especially necessary since the therapy that is usually provided (diuretics) must decrease plasma volume to achieve the desired reduction in pulmonary capillary pressure. If a patient does not have an elevated hydrostatic pressure, the therapeutic depletion of plasma volume can result in iatrogenic hypovolemic hypoperfusion.

Patients who develop hydrostatic pulmonary edema should have a reason to have heart disease, either prior to the respiratory distress or as an acute new illness. (A patient without heart disease would, of necessity, have to be in severe, oliguric renal failure to develop hydrostatic edema from fluid infusion alone.)

Attributing respiratory distress to hydrostatic edema demands the precision of making a heart failure diagnosis. As described in chapter 3, congestive heart failure is a hemodynamic alteration characterized by features such as tachycardia, an increased or well maintained blood pressure, jugular venous distention, and auscultation of an S3 gallop. None of these diagnostic parameters are linked to the lungs or fluid sequestration per se. Using the lungs and fluid sequestration for hemodynamic diagnoses can be dangerously misleading.

Furthermore, making proper hemodynamic diagnosis is particularly germane to the management of indirect ALI and ARDS (see below). Again, if the clinician decides to provide therapy for hydrostatic pulmonary edema, then confirmation of heart disease either by preceding information or newly acquired data should accompany that management strategy.

Curiously, indirect ALI and ARDS often result in little chest physical findings save for evidence of respiratory distress. A few "crackles" and wheezes may be present, but flagrant bubbling breath sounds are uncommon. Consolidation by physical examination (vesicular-tubular or tubular breath sounds) can sometimes be discerned, especially in the sedated, intubated, mechanically ventilated patient.

The diagnosis of ALI and ARDS demands evidence of severe oxygenation alterations. Typically, these deficits result in mechanical ventilation, especially for ARDS. In contrast, hydrostatic edema dis oxygenation is usually managed with the administration of nasal or face mask oxygen. Therefore, if poor oxygenation is the principal indication for mechanical ventilation, the diagnosis of hydrostatic pulmonary edema as the primary disorder is less likely (44).

Routine chest x-ray findings do not regularly allow a distinction between hydrostatic and non-hydrostatic mechanism of lung water accumulation. Relatively low-contrast resolution and two-dimensional representation of three-dimensional anatomy can confound the distinction of the site and magnitude of pulmonary parenchymal pathology. In comparison, the higher resolution and cross-sectional images of the chest CT can differentiate the more common perihilar, central vascular, and parenchymal alterations of hydrostatic edema (bat-wing alterations) with those of the more patchy and dependent changes characteristic of ARDS (45–47).

Invasive hemodynamic monitoring with a pulmonary artery catheter (PAC) can assist with the diagnosis, recognizing that it is possible to have elevated hydrostatic pressures and direct or indirect lung injury simultaneously. The PAC data, specifically pulmonary artery occlusion pressures (PAOP) must be juxtaposed to the known effects of hydrostatic pressure on the normal lung (Table 6.7). For instance, while a PAOP of 20 mm Hg is higher than normal, this elevation does not typically result in severe bilateral dense alveolar infiltrates. Dense alveolar infiltrates and, especially, poor oxygenation (PaO_2/FiO_2, <200 mm Hg) would not be readily explained by this hydrostatic pressure, and further consideration of other mechanisms of pulmonary malfunction would be warranted.

Management of ALI and ARDS

The mechanical ventilator management of ALI and ARDS is described in the section on "Mechanical Ventilation". This section will focus on the principles listed in Table 6.13.

As mentioned above, the realization that respiratory distress is secondary to a direct lung injury should link to a therapeutic plan specific to that insult (i.e., pneumonia, pulmonary contusion, pulmonary embolism, etc.) Similarly, recognition of the mechanism of indirect injury (i.e, pancreatitis, perforated diverticulitis, etc.) should prompt specific therapeutic decision making.

In addition to addressing the principal cause of ALI and ARDS, strategies related to fluid management and amelioration of systemic inflammation are active management considerations that have been under investigation for decades.

Since, by definition, ALI/ARDS is not hydrostatic pulmonary edema, fluid management concepts have been linked to the theoretical benefits and detriments of crystalloid versus colloid infusion. While colloid administration characteristically results in less total body fluid accumulation, does an elevated oncotic pressure also result in diminished lung fluid accumulation and improved lung function in the setting of ALI/ARDS?

Human studies since 1983 have demonstrated no improvement in physiologic shunt, nor EVLW with colloid administration whether or not the study fluids were administered to treat the lungs or the circulation (11,48,49). In one study, the combination of albumin and diuretic administration in patients with a normal cardiac index did result in an increase in PaO_2/FiO_2 as compared to a decrease with diuretics alone. Curiously, cardiac index also increased with albumin and diuretic combination and decreased in the diuretic-only group. Since Qs/Qt was not calculated, it is possible that the improved arterial oxygenation was secondary to the higher

Table 6.13 Management Principles for Acute Lung Injury and Acute Respiratory Distress Syndrome

I. Treat the underlying cause
  A. Direct
    i. Pneumonia
    ii. Aspiration
    iii. Pulmonary contusion
    iv. Pulmonary embolism
    v. Inhalation injury
    vi. Near-drowning
  B. Indirect
    i. Systemic sepsis
    ii. Pancreatitis
    iii. Multiple trauma
    iv. Ischemia/reperfusion
    v. Massive transfusion
    vi. Transfusion-associated lung injury
    vii. Fat embolism syndrome
II. Fluid management
  A. Type of fluid
  B. Volume of fluid
III. Treatment of systemic inflammation
  A. Rapid restoration of the circulation
  B. Anti-inflammatory agents

cardiac index and a resultant increase in mixed venous oxygen saturation rather than an improvement in lung physiology per se (50).

Fluid management for ALI/ARDS is intimately associated with the evaluation and treatment of circulation deficits. This association has prompted study of circulation monitoring, especially the potential advantages or disadvantages of pulmonary artery catheter (PAC) placement as well as "liberal" versus "restrictive" fluid administration strategies.

As described in the chapters 2–4, a treatment that promotes migration from the Ebb Phase (hypodynamic, decreased oxygen delivery, and consumption) of shock to the Flow Phase (hyperdynamic, increased oxygen delivery, and consumption) provides a survival benefit. Clinical investigation has repeatedly demonstrated that "forcing" a hyperdynamic circulation using vasoactive drugs does not predictably result in increased oxygen consumption for the entire group in the study. Likewise, however, it is just as unpredictable to determine which individual patient will or will not respond to the circulatory augmentation. Therefore, the "bottom line" for shock assessment is the influence of a management strategy on oxygen consumption (51,52). If this feature is not addressed (at least with surrogates like lactic acid and venous oxygen saturation), then the value of the acquired circulatory data is speculative (53,54).

In addition, resuscitation from shock is achieved when the Flow Phase is documented. For many decades, a cardiac index ≥4.0 L/min/m^2, measured with a PAC, has been indicative of the hyperdynamic circulation consistent with the Flow Phase. Therefore, investigations that principally include patients exhibiting a hyperdynamic circulation are not likely to demonstrate an advantage from circulatory adjustment using PAC data.

Several recent publications suffer from these deficits. To summarize the principle, data supported findings are as follows:

1. Placement and use of a PAC is not dangerous (55).
2. Use of a PAC in hyperdynamic patients without any attention to oxygen delivery and consumption parameters 48 hours after the onset of ARDS is no better than using a CVP monitor of the circulation (56).
3. After achievement of the Flow Phase, it is not necessary to further augment intravascular volume during the next seven days in patients with ARDS. If an iso fluid balance

(–136 ± 491 ml/7 days) strategy is employed in the Flow Phase as compared to allowing further fluid sequestration (6,992 ± 502 ml/7 days), then a decrease in two ventilator and ICU days can result (57,58).

Please note that a restrictive fluid management strategy does not apply to patients in the Ebb Phase. The clinician should not prevent a patient from achieving Flow Phase status because of an overwrought concern about the duration of ventilator support (58).

Since indirect ALI/ARDS is a consequence of systemic inflammation, the general principles for limiting the organ damaging effects of systemic inflammation apply as previously emphasized in chapter 4. Once again, rapid migration from the Ebb Phase to the Flow Phase of inflammatory shock has been demonstrated to diminish the blood concentration of proinflammatory mediators that have been implicated in the pathogenesis of ALI/ARDS (27,59).

Most of the additional attempts to limit the effects of systemic inflammation on the lung (i.e., antioxidants, thromboxane inhibition, inhaled nitric oxide, inhaled Albuterol) have not been effective (60). Still of interest is the use of glucocorticoids and enteral feeding enriched with particular nutrients.

Supraphysiologic dosing (>300 mg/day hydrocortisone equivalent) of glucocorticoids has been employed in the early (exudative phase) as well as the middle (proliferative phase) of ALI/ARDS with data and analysis that allow for both proponents and detractors (27,60). Similar to the concept of the "eucorticoid state" described in chapter 4, the most effective glucocorticoid dosing may demand titration to markers of systemic and/or local inflammation to promote improvement in organ function while allowing host-defense and wound healing processes to continue. At this point, the published dosing regimens, on average, appear to promote this balance with no worrisome risk of infection and/or neuromuscular disturbance (27,61).

Enteral feeding has distinct host-defense advantages as compared to parenteral nutrition. Local host defenses (mucosal barrier function) as well as systemic defenses (stimulation of the gut-associated lymphatic tissue) have been documented (see chap. 8). More controversial has been the proposal that certain nutrients can limit the detrimental effects of systemic inflammation. Human investigation supports the enteral administration of omega-3 fatty acid from fish oil, whereas other nutrients (glutamine, arginine, antioxidant vitamins, etc.) are not consistently helpful. Lung parameters such as PaO_2/FiO_2, compliance, and ventilator duration have all improved with this supplement (62–65).

Chest Trauma

Chest trauma may result in any or all of the conditions listed in Table 6.14, many of which are managed with tube thoracostomy alone. Respiratory failure that results in mechanical ventilation is most commonly secondary to multiple rib fractures (mechanical failure—poor carbon dioxide elimination) and/or pulmonary contusions (alveolar failure—poor oxygenation).

Flail chest is defined as instability of the chest wall that allows paradoxical movement of a chest wall segment (inward movement during inspiration). This usually requires at least three ribs broken in two places. The most common mechanism for flail chest is a blow to the lateral thoracic cage, which produces anterior and posterior fractures. The association of lung contusion with flail chest results from the close apposition of the lung to the force of injury. Single, lateral rib fractures are most often secondary to anterior and/or posterior forces that cause the lateral stress on the ribs and usually little parenchymal insult.

With rib fractures, the patient may be tachypneic, splinting the affected area, and exhibit marked tenderness and/or bony crepitus at the injury site. With flail chest tachypnea, splinting and tenderness will be noted along with paradoxical chest wall movement. Physical examination will also be altered by concomitant processes such as pneumothorax and hemothorax.

Mechanical ventilation is employed only when either or both mechanical lung and alveolar lung function are inadequate. The simple presence of a flail chest does not mandate mechanical ventilation. In fact, more often contusion-associated alveolar malfunction is a greater problem than mechanical instability. Frequently, a simple mechanical failure can be ameliorated by adequate pain relief (e.g., rib blocks, epidural and paravertebral anesthesia) (66–68).

Table 6.14 Chest Trauma

- Rib fractures
- Flail chest
- Pulmonary contusion
- Pneumothorax
- Tension pneumothorax
- Hemothorax
- Ruptured thoracic aorta
- Penetrating thoracic visceral injury
- Blunt myocardial injury

Table 6.15 Clues to Aortic Rupture

- Mechanism of Injury
- Wide mediastinum
- First rib fracture
- Apical CAP
- Nasogastric tube deviation
- Hypertension
- Depressed left main stem bronchus

Mechanical stabilization of the thorax is gaining popularity for mechanical failure that persists a few days after chest injury (69–71).

Pulmonary contusion is the most common mechanism for alveolar failure after blunt chest trauma. The lung parenchymal injury that follows the shearing, bursting, stripping, and implosion effects of energy transfer incites hemorrhage and an acute inflammatory response that result in varying degrees of intrapulmonary shunt and the necessity of mechanical support. On average, the more pulmonary parenchyma damage (>28% by CT imaging) occurs, the more likely is the need for mechanical ventilation, but sometimes a slight injury is associated with poor oxygenation, whereas a marked injury is not (72,73).

Chest CT is much more sensitive than plain chest x-ray for identifying pulmonary contusion, and the mere presence of a contusion does not demand ventilator management, but demands the anticipation that pulmonary function may worsen over the next several hours.

The management of pulmonary contusion is supportive with the expectation that resolution will at least start to become evident by post injury days 3–5. Since injured pulmonary parenchyma exhibits less robust host-defense mechanism as compared to normal lung, infection (i.e., nosocomial pneumonia) at the site of contusion is a common mechanism for lack of resolution and/or progression of malfunction (72,73).

Severe blunt thoracic injury, especially secondary to deceleration, is associated with thoracic aorta rupture. This diagnosis may not have been entertained until the patient arrives in the ICU. Of all the clinical clues listed in Table 6.15, the mechanism of injury should alert the clinician the most that the thoracic aorta requires investigation. The chest CT used commonly as part of trauma evaluation is sufficient to locate the site of injury and has replaced angiography and transesophageal echocardiography as a sensitive and specific diagnostic method (74,75). The initial management is "controlled hypotension" and bradycardia using a combination of beta blockade and vasodilator administration, similar to the plan for aortic dissection. Most often, this is followed by surgical repair, with the endovascular approach becoming more commonplace (74,75).

Cardiac injury following blunt trauma (blunt myocardial injury, BMI) is a particularly enigmatic diagnosis. Perfect diagnostic specificity demands demonstration of an anatomical injury to the heart such as contusion, chamber rupture, and papillary muscle disruption. While chamber rupture with pericardial fluid and loss of papillary muscle integrity with valvular regurgitation might be evident by echocardiography, these are extremely rare (76). Instead,

Table 6.16 Diagnostic Features of Blunt Trauma Cardiac Injury

I.	ECG alterations—most often arrhythmias
II.	Cardiac troponin elevations
III.	Regional or global contractile abnormalities (echocardiogram)

Table 6.17 Pneumonia Risk Factors

- Colonization of oropharynx
- Intubation of trachea
- Depressed immunocompetence
- Previous antibiotic exposure
- Increased stomach flora
- Aspiration
- Pulmonary contusion
- Pulmonary edema (any etiology)
- Blood transfusion
- Systemic inflammation

more subtle clues of myocardial insult have been evaluated (Table 6.16) (77). Importantly, systemic inflammation can also cause all these findings (see chap. 4) as can brain injury (see chap. 9). Consequently, the specificity of any of these diagnostic modalities must be questioned in the severely injured individual.

Regardless of diagnostic specificity, abnormalities in any of these diagnostic tests place the patient at risk for additional cardiac morbidity (78). Therefore, patients considered at risk can be screened, typically with an ECG and troponin measurement, realizing that repeat studies in 4–6 hours increase the sensitivity (79). A positive screening test can then be augmented by an echocardiogram to evaluate for the presence of gross anatomical alterations.

Management of arrhythmias and poor myocardial contractility from BMI is the same for these disturbances associated with other pathology (see chap. 3). Irrespective of the principal mechanism, the cardiac abnormalities are usually transient (hours to days). Obviously, the most severe anatomical alterations can result in the need for acute surgical intervention (valve repair, repair of chamber rupture) or result subsequently in delayed valvular, septal, or myocardial wall disturbances (76,77).

Pneumonia and Empyema

Pneumonia while on a ventilator [ventilator-associated pneumonia (VAP)] is a frequent cause of new or continuing respiratory failure in surgical ICU (SICU) patients. Attributable mortality estimates of 30–40% emphasize the importance of this insult in surgical critical illness (80,81). Risk factors that promote parenchymal lung infection in the SICU are listed in Table 6.17 (80,82–84). Nosocomial organisms may colonize the oropharynx of the critically ill patient in 24 hours. Intubation of the trachea bypasses a normal barrier to the migration of organisms and may reduce ciliary propulsion of organisms cephalad. Critical illness globally diminishes immunocompetence, which enhances the progression of colonization to invasion. Previous antibiotic use often suppresses endogenous flora increasing the concentration of resistant organisms from the environment (*Serratia*, *Pseudomonas*, *Enterobacter*, *Haemophilus influenzae*) and endogenous flora (*Escherichia coli*, *Klebsiella*). Intubation of the trachea with endotracheal or tracheostomy tube balloon inflation does not protect fully against aspiration of small amounts of either oropharyngeal or gastric contents (85,86).

The role of stress ulcer prophylaxis with control of acid production in the stomach in the development of ICU pneumonia is controversial (84,87,88). Presumably, control of acid allows for more rapid growth of potential pathogens in the upper GIT as compared with no prophylaxis.

Table 6.18 Pneumonia Diagnostic Criteria

- Elevated temperature
- Elevated WBC
- Consolidation on physical examination
- Positive sputum culture
- Many polys on Gram stain of sputum
- Consistent infiltrate on CXR

Table 6.19 Diagnostic Tools for Pneumonia

1. Bronchoscopic sampling for quantitative culture, no protected brush (sensitivity 100%, specificity 100% - one report)
2. Bronchoscopic-protected brush specimen (PBS) quantitative culture (sensitivity 38–100%, specificity 60–100%)
3. Non-bronchoscopic protected brush specimen
4. Bronchoscopic bronchoalveolar lavage (BAL) quantitative culture (sensitivity 72–88%, specificity 71–100%)
5. Directed (left or right lung) wedged suctioning without bronchoscopy—not quantitative
6. Non-directed endotracheal aspiration—quantitative
7. Lung biopsy

This augmented growth would then allow more vigorous colonization of the "aerodigestive tract" and promote pulmonary invasion. Possibly, more important than this controversy is discerning which patients are at risk for stress ulceration/gastritis and limiting prophylaxis to that group (see chap. 8).

Arising commonly in the milieu of other etiologies of surgical sepsis, the diagnostic and therapeutic challenges in VAP can be large. Proposed diagnostic criteria are listed in Table 6.18. These are especially useful when no pulmonary insult has predated the suspicion of pneumonia. Diagnosis of pneumonia can be especially difficult when the lung has already suffered a non-infectious insult (e.g., aspiration, pulmonary contusion, ARDS, cardiogenic pulmonary edema) that promotes subsequent bacterial invasion, yet it can be responsible for continuing pulmonary infiltrates. Under these circumstances, the use of expectorated or suctioned sputum, fever, and elevation of white blood cells are not sufficiently specific to allow the confirmation of pneumonia. Therefore, other techniques have been proposed to increase specificity in those patients with infiltrates, sputum cultures with pathogens, and signs of systemic inflammation (Table 6.19).

None of these modalities have been proven to provide sufficient sensitivity and specificity to become commonplace (84,89). Especially illustrative of the diagnostic challenge for VAP is the report that pathologists do not agree when asked to distinguish the presence or absence of histologic pneumonia (89,90).

In general, it is detrimental to patient outcome to either under diagnose or over diagnose pneumonia. Under diagnosis can result in progressive lung damage and, possibly, death. Over diagnosis and subsequent treatment can result in antibiotic toxicity and superinfections with resistant organisms. One diagnostic and therapeutic tactic has been advocated in the use of the Clinical Pulmonary Infection Score (CIP-IS) to make a VAP diagnosis (Table 6.20). This is less invasive and may provide sufficient information to initiate as well as discontinue antibiotics (89,91).

After the diagnosis of VAP is made, treatment should be directed whenever possible at the organism(s) known to be responsible for the pneumonia. VAP can be polymicrobial and, therefore, choosing to treat only one of several pathogens found through microbiologic analysis is illogical unless some additional information (positive blood culture, pleural fluid culture) identifies a single pathogen.

Common bacterial pathogens are listed in Table 6.21. When a patient demonstrates signs of severe systemic inflammation broad-spectrum therapy, which includes antimicrobials

effective against nosocomial *Staphylococcus aureus* and the most prevalent nosocomial Gram-negative organisms, is warranted until more specific microbiologic data are available, at which time more precise therapy may be provided.

Obviously, prevention of VAP precludes the necessity of specific diagnosis and treatment. Effective VAP prevention is now becoming incorporated into intensive care protocols (Table 6.22) (88).

Empyema must be considered in any patient who shows clinical signs of sepsis and evidence of a pleural effusion. Risk factors for empyema are listed in Table 6.23. In trauma patients, chest tubes are often hurriedly inserted as a life-saving procedure, with less-than-ideal sterile technique, into bloody fluid. Elective chest tube placement at the time of pulmonary surgery is much less likely to be contaminated.

Table 6.20 Clinical Pulmonary Infection Score Calculation[a,b]

Temperature (°C)
≥36.5 and ≤38.4 = 0 point
≥38.5 and ≤38.9 = 1 point
≥39 and ≤36 = 2 points
Blood leukocytes, mm^3
≥4,000 and ≤11,000 = 0 point
<4,000 or >11,000 = 1 point + band forms ≥50% = add 1 point
Tracheal secretions
Absence of tracheal secretions = 0 point
Presence of non-purulent tracheal secretions = 1 point
Presence of purulent tracheal secretions = 2 points
Oxygenation: PaO_2/FIO_2, mm Hg
>240 or ARDS (ARDS defined as PaO_2/FIO_2, or equal to 200, pulmonary arterial wedge pressure
≤18 mm Hg and acute bilateral infiltrates) = 0 point
≤240 and no ARDS = 2 points
Pulmonary radiography
No infiltrate = 0 point
Diffuse (or patchy) infiltrate = 1 point
Localized infiltrate = 2 points
Progression of pulmonary infiltrate
No radiographic progression = 0 point
Radiographic progression (after CHF and ARDS excluded) = 2 points
Culture of tracheal aspirate
Pathogenic bacteria[c] cultured in rare or light quantity or no growth = 0 point
Pathogenic bacteria cultured in moderate or heavy quantity = 1 point
Same pathogenic bacteria seen on Gram stain, add 1 point

[a]Modified from Ref. (8).[b]CPIS at baseline was assessed on the basis of the first five variables, that is, temperature, blood leukocyte count, tracheal secretions, oxygenation, and character of pulmonary infiltrate. CPIS at 72 hours was calculated based on all seven variables and considered the progression of the infiltrate and culture results of the tracheal aspirate. A score >6 at baseline or at 72 hours was considered suggestive of pneumonia.[c]Predominant organism in the culture.*Abbreviations*: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; PaO_2/FIO_2, ratio of arterial oxygen pressure to fraction of inspired oxygen.

Table 6.21 Common Pathogens in Surgical Intensive Care Unit Pneumonia

- *Pseudomonas*
- *Enterobacter*
- *Serratia*
- *Staphylococcus aureus*
- *Klebsiella*
- *Escherichia coli*

After previous pulmonary pathology, chest injury, and/or thoracic surgery, distinguishing pleural fluid from infiltrates and thickened pleura may be impossible with standard chest radiography. In this setting, chest ultrasound and/or CT have proved useful for locating and sampling suspicious collections.

Effusions can be transudative or exudative, but infected pleural fluid will exhibit exudative characteristics. Empyema is distinguished from less severe infectious exudates by the presence of gross pus (Table 6.24) (92).

Empyema therapy requires external drainage and sometimes decortication (removal of the surrounding fibrous capsule to allow full expansion of the lung) to eradicate the infectious focus (92).

Pulmonary Embolism

Pulmonary thromboembolism (PE) is most commonly secondary to lower extremity and pelvic deep venous thrombosis (DVT). Upper extremity clot can also be responsible, albeit much less frequently (93). Of note is the disturbing finding in trauma patients that PE may develop without locating a site of DVT formation (94).

Classic factors that predispose to DVT are described in Table 6.25. Trauma refers to direct injury to a vein. Stasis refers to diminished blood flow in a vein. Hypercoagulable states can be present because of underlying disease (i.e., malignancy, protein C deficiency), but more commonly follows tissue injury distant from the deep vein proper.

Table 6.22 Strategies to Prevent Ventilator-Associated Pneumonia

I.	Removal of endotracheal tube as soon as possible
II.	Use of a formal infection control program
III.	Adequate hand washing
IV.	Semirecumbent positioning
V.	Chlorhexidine oral rinse
VI.	Avoidance of gastric distention
VII.	Continuous subglottic suctioning

Table 6.23 Empyema Risk Factors

- Pneumonia
- Chest tube, trauma
- Esophageal injury

Table 6.24 Distinguishing Infected Pleural Exudates

Characteristic	Uncomplicated parapneumonic effusion	Complicated parapneumonic effusion	Empyema
Appearance	Slightly turbid	Cloudy	Pus
Biochemistry values pH	>7.30	<7.20	NA
Glucose level, mg/dL	>60	<40	
Ratio of pleural fluid to serum glucose	>0.5	<0.5	NA
Lactate dehydrogenase level, U/L	<700	>1,000	NA
Polymorphonuclear leukocyte count, cells/μL	<15,000	>25,000	NA
Microbiologic test result	Negative	May be positive	May be positive

Abbreviation: NA, not applicable.

Table 6.25 Virchow's Triad

- Trauma
- Stasis
- Hypercoagulable state

Table 6.26 Risk Factors for Deep Venous Thrombosis in Critical Illness

Age >50
Severe trauma
Length of ICU stay
Mechanical ventilation
Sedation/paralysis
Emergency interventions
Femoral vein catheter placement
Malignancy
Obesity

Table 6.27 Diagnosis of Deep Venous Thrombosis

1. Physical examination
   - Unilateral edema
   - Painful calf to palpation
   - Pain on dorsiflexion of foot
2. Laboratory
   - Venous duplex ultrasound
   - Venogram

The incidence of DVT in critically ill surgical patients is estimated to be 30–58% in patients who do not receive thromboprophylaxis, but at least 10% in individuals receiving low-dose anticoagulation. Risk factors associated with DVT are listed in Table 6.26 (95,96). Among trauma patients, those with spine fractures and paraplegia, as well as those with lower extremity injuries, are particularly at risk.

The diagnosis of DVT is suggested by the physical examination findings listed in Table 6.27. The high false-negative and false-positive rate for physical examination stresses the importance of a high index of suspicion and a willingness to obtain more objective studies (97). Today, venous duplex is the most common investigation, but it may not detect pelvic thrombosis and PE can certainly occur in the absence of an identified lower extremity DVT (98).

During surgical critical illness, PE is often diagnosed on the basis of a high index of suspicion, although history, physical examination, and simple tests may be reasonably conclusive when gross findings are evident (Table 6.28). Since surgical critical illness is often associated with coagulation alterations, the use of the D-dimer assay is of little value (99–101). Multidetector chest CT has become the preferred diagnostic modality, but negative studies must be juxtaposed to the magnitude of clinical suspicion. Pulmonary angiogram can be used when the chest CT is negative despite a high clinical suspicion (100,102).

The most common arterial blood gas alterations include a decrease in both PaO_2 and $PaCO_2$. These alterations are difficult to explain from the mechanical effect of the embolic clot.

Obstruction of pulmonary blood flow to well-ventilated lung should result in an increase in VD with little effect on PaO_2, and possibly an increase in $PaCO_2$. When measured, physiologic VD can increase, but the stimulus to increase VT and rate most often overcomes the augmented VD (103). This may not be the case in patients with increased physiologic VD from a pre-existing illness (for instance chronic obstructive pulmonary disease). In these patients, PE can be considered as a mechanism of increasing $PaCO_2$.

Table 6.28 Diagnosis of Pulmonary Embolism

1. History
   - Chest pain
   - Hemoptysis
   - Dyspnea
2. Physical examination
   - Pleural friction rub
   - Accentuated pulmonic second heart sound
3. Laboratory
   - Decreased PO_2
   - Decreased PCO_2
   - Clear CXR, rare Westermark Sign
   - Positive chest CT scan
   - Positive pulmonary angiogram

Why does the PaO_2 decrease? A fall in PaO_2 implies a decrease in the ventilation to perfusion ratio that emulates a physiological shunt. As stated in the section on "Determinants of PaO_2 and $PaCO_2$," the normal lung pulmonary blood flow matches ventilation despite variation in both of these parameters in both vertical and horizontal planes (5). Pulmonary emboli are characteristically lodge in regions of high perfusion that should be linked with areas of high ventilation. Diversion of pulmonary blood flow from such areas of high ventilation to normal regions of lung that receive less ventilation would result in a decreased V/Q ratio akin to a physiologic shunt. Such a mechanism has been demonstrated experimentally (Fig. 6.10) (104).

Hemodynamic alterations are primarily linked to the magnitude of pulmonary artery obstruction and consequent right ventricular impairment. Pulmonary vascular resistance can also be increased by hormonal (i.e., histamine, kinins) and hypoxic vasoconstriction mechanisms. Sufficient dilation of the right ventricle can impair left ventricular filling and coronary perfusion (105).

The therapy of submassive PE is listed in Table 6.29. Surgical patients can usually receive anticoagulation (heparin—either unfractionated or fractionated) unless the risk of hemorrhage at the surgical site is life threatening (e.g., intracranial surgery). The physiology of PE may be ameliorated with heparin, but mostly the physiology abates as part of the natural history of the disease, and anticoagulation is used primarily to prevent further clot propagation and migration at the initial DVT focus. The use of thrombolytic therapy has not been shown to result in a durable benefit when used for submassive embolism (101).

Anticoagulation will usually suffice to prevent further emboli, but if anticoagulation fails to be protective and/or continued anticoagulation is contraindicated, then placement of an inferior vena cava (IVC) filter is the option of choice, presuming that the thromboembolism originated below the renal veins.

Massive PE with hypotension, marked right ventricular dilation on an echocardiogram, and/or measurement of a low cardiac index (<2.0 $L/min/m^2$) is a prompt for thrombolysis (e.g., alteplase). Augmenting right ventricular filling may provide temporary improvement, but the short-term infusion (2 hours or less) of a thrombolytic is recommended along with the continuation of unfractionated heparin for both a rapid and durable effect (101,106). Intracranial pathology, uncontrolled hypertension (unlikely in this setting), and recent major surgery or trauma are considered contraindications for thrombolysis. As with all management decisions, the clinician must weigh the risk-benefit circumstances in that bleeding from an accessible surgical site (e.g., recent colectomy) might be preferable to certain death from a massive PE. Once as massive embolism has threatened a patient, commonly, an IVC filter is placed in conjunction with ongoing anticoagulation.

Prophylaxis strategies against DVT and subsequent PE in critically ill patients are outlined in Table 6.30. Providing an effective DVT prophylaxis algorithm is particularly challenging in trauma patients. High-risk trauma patients include those with severe closed-head trauma (Glasgow Coma Scale <8), spinal injury with paraplegia or tetraplegia, complex pelvic fractures,

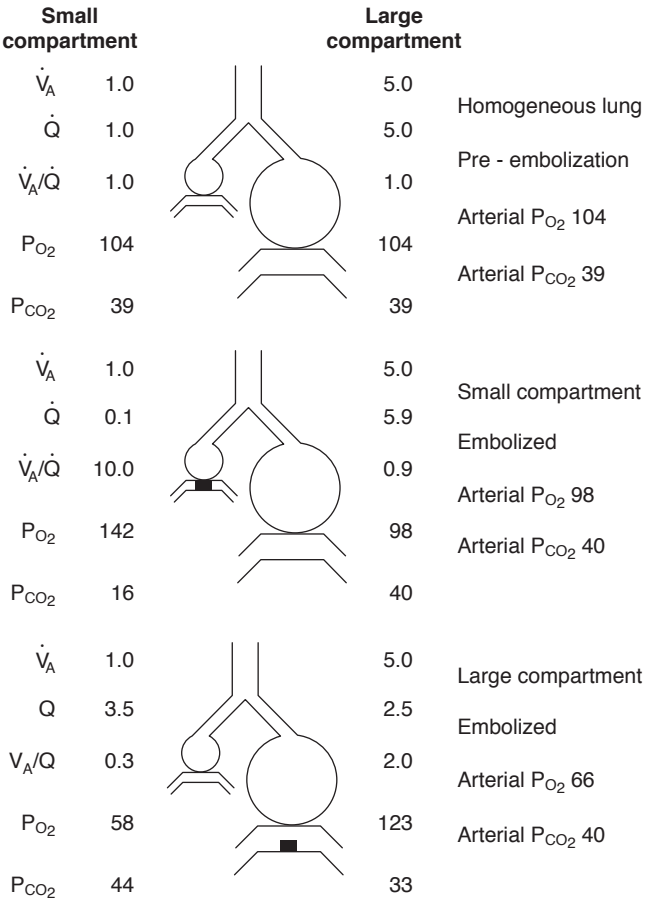

Figure 6.10 Two-compartment lung model with an area of large ventilation and perfusion as well as small ventilation and perfusion. In the upper panel, ventilation and blood flow are matched in both compartments. In the middle panel, blood flow to the small compartment has been reduced by 90% and diverted to the large compartment. This results in a small increase in dead space and slight increase in shunt. In the bottom panel, blood flow to the large compartment has been decreased by 50% and diverted to the small compartment. This results in a decrease in the V/Q relationship in the small compartment and an increase in physiologic shunt. *Source*: From Ref. 104.

Table 6.29 Treatment of Submassive Pulmonary Embolism

- Anticoagulation
- Thrombolytic agents
- Prevent future emboli

Table 6.30 Deep Venous Thrombosis and Pulmonary Embolism Prophylaxis

- Intermittent pneumatic compression
- Anticoagulation
  - –Low-dose unfractionated heparin
  - –Low molecular weight heparin
  - –Warfarin
- Inferior vena cava filter

multiple long bone fractures, and massive transfusion. Compared with other surgical patients, low-molecular-weight heparin (LMWH) has been shown to be superior to unfractionated heparin (UFH) in trauma patients, but the fear of hemorrhage has resulted in the recommendation to delay administration in these high-risk groups. One recommendation is to provide prophylaxis dosing within 24 hours following solid organ injury and within 72 hours for head trauma (96). Another study suggested that prophylaxis in head trauma patients is safer after a follow-up head CT shows no progression of hemorrhage, especially when the abbreviated head injury score was <5 (see chap. 9) (107).

Effective dosing of LMWH in trauma is also a challenge. Monitoring with antifactor Xa levels suggests that underdosing is common, and monitoring with thromboelastography suggests that antifactor Xa levels are not sufficiently specific to determine adequate effect. Therefore, continuing investigation is needed to sort out the most effective and safe timing and dosing of LMWH in critically ill surgical patients (108,109). In the meantime, guidelines are available that provide a workable consensus (96).

More controversial than LMWH issues is the use of IVC filter placement for prophylaxis. All trauma patients considered at high risk for DVT are at risk for hemorrhage with anticoagulation. Individual care decisions for such patients have included the placement of permanent and, more recently, retrievable IVC filters. Reports of IVC filter placement usually include patients who were treated for a known DVT and/or PE, making analysis of prophylaxis difficult. Again, published guidelines provide an acceptable algorithm pending more clinical investigation (96,110,111).

Mechanical Ventilation

Since respiratory failure may occur primarily from mechanical or alveolar failure, mechanical ventilation may be used to improve pulmonary function related to one or both of these mechanisms (Table 6.31). Mechanical ventilation can improve ventilation in patients with increased work of breathing, decreased function of respiratory muscles, or disease related high V_D/V_T. This results in improved $PaCO_2$. Mechanical ventilation can also open collapsed alveoli, improve FRC, and decrease physiologic shunting, thereby improving PaO_2.

Some Basics

Positive pressure ventilation expands the lung by increasing the pressure in the airway as compared to the pressure in the alveolus. The airway and the lungs/chest wall components of the pulmonary "system" are in series such that the pressure (P) needed to provide airflow must overcome the resistance in the airway (P_{res}) and the elastic recoil of the lungs/chest wall ($P_{elastic}$). The pressure needed to move fluid in a tube is directly related to the resistance (R) in the tube and the flow of the fluid: $P_{res} = Flow \times R_{aw}$ where aw = airway. The pressure needed to expand a space by a certain volume (ΔV) is determined by that volume change and the compliance of the space. Compliance = $\Delta V/\Delta P$. Therefore, $P_{elastic} = \Delta V/C_{rs}$, where C_{rs} is the compliance of the lungs/chest wall.

The relationship of flow to P_{res} and $P_{elastic}$ is shown in Figure 6.11. The most common flow provided by a mechanical ventilator is constant flow, and the initial rapid increase in airway pressure is the pressure needed to overcome airway resistance. The slower, more gradual increase in airway pressure is the pressure needed to expand the lungs and chest wall (8).

Table 6.31 Indications for Mechanical Ventilation

1. Mechanical ventilatory failure (ventilation)
   - Excess work of breathing
   - Cannot exhale carbon dioxide
2. Alveolar failure (oxygenation)
   - Decrease in FRC
   - Atelectasis

Applying a pressure to overcome resistance and elastic recoil will result in a change in lung volume (Fig. 6.12). Normally, peak airway pressure is greater than peak alveolar pressure (plateau pressure). As described in Figure 6.7, holding a pressure during inspiration (inspiratory hold) allows measurement of plateau pressure. Normally, expiratory flow ends before the next inspiratory cycle (Fig. 6.12). If expiration is delayed or if the inspiratory cycle is too rapid, pressure can develop in the lung parenchyma (auto-positive end expiratory pressure, auto-PEEP) that is recognized during an expiratory hold (Fig. 6.13). More often, PEEP is a chosen setting on the ventilator that improves FRC. Since normal expiration meets some expiratory resistance in the larynx, an endotracheal tube and a tracheostomy can result in loss of this resistance such that the end-expiratory pressure is lower than that during spontaneous, negative

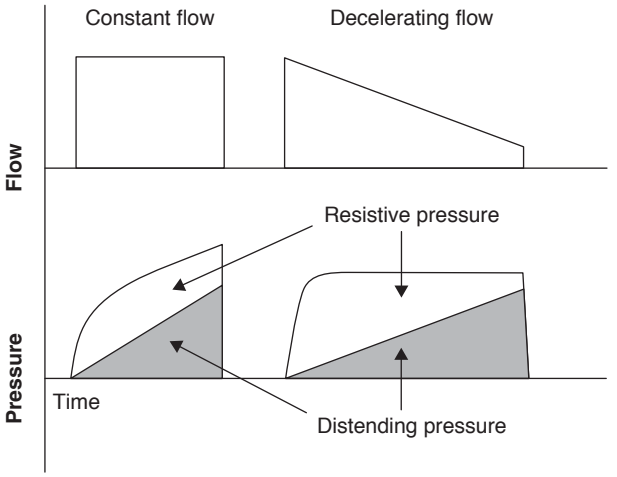

Figure 6.11 Flow-pressure waveforms. The left tracing represents a constant or square waveform. When flow is delivered at a constant rate, resistive pressure remains constant while distending pressure increases with the delivery of the tidal breath. In the right tracing, decelerating flow is shown. With decreasing flow, resistive pressure decreases as distending pressure increases. This results in a constant pressure during the tidal breath. *Source*: From Ref. 8.

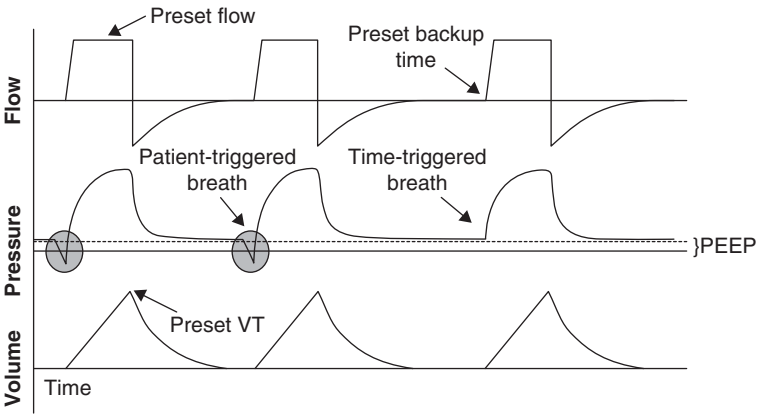

Figure 6.12 Flow, pressure, and volume information using a ventilator in assist-control mode. The first two breaths are initiated by the patient via a drop in airway pressure (circled). The breath is delivered by constant flow. Flow lasts until a preset tidal volume (VT) is reached. The exhalation port of the ventilator then opens and the patients exhales. In the third breath, the preset backup time limit is met (the patient did not initiate a breath) and the ventilator delivers a breath (mandatory ventilation). *Source*: From Ref. 8.

pressure breathing. An application of "physiologic PEEP", then, is common (usually 5 cm H_2O) in mechanical ventilator settings (Fig. 6.13) (8).

Common Ventilator Modes

Common ventilator modes are listed in Table 6.32. During volume-limited controlled mechanical ventilation (CMV) the only ventilator "events" are those programmed into the ventilator. This mode is present when patients are paralyzed. Typically, the VT (8–10 ml/kg, respiratory rate (10–12/min), and constant flow rate (60 L/min.) are selected by the care giver and the patient cannot waiver from those settings. In assist control (AC) mode, the patient initiates a negative inspiratory effort that triggers the action of the ventilator. If the patient does not initiate a breath, then a "backup" rate is in place, resulting in the equivalent of CMV (Fig. 6.12). Once again, the volume is selected rather than the pressure (8).

During synchronized intermittent mandatory ventilation (SIMV), the ventilator delivers a mandatory breath in synchrony with the patient's inspiratory effort, like AC. However, depending on the set respiratory rate, the patient can initiate an unsupported breath(s) between the ventilator assist episodes (Fig. 6.14**)**. The patient-initiated breaths can be pressure supported (112).

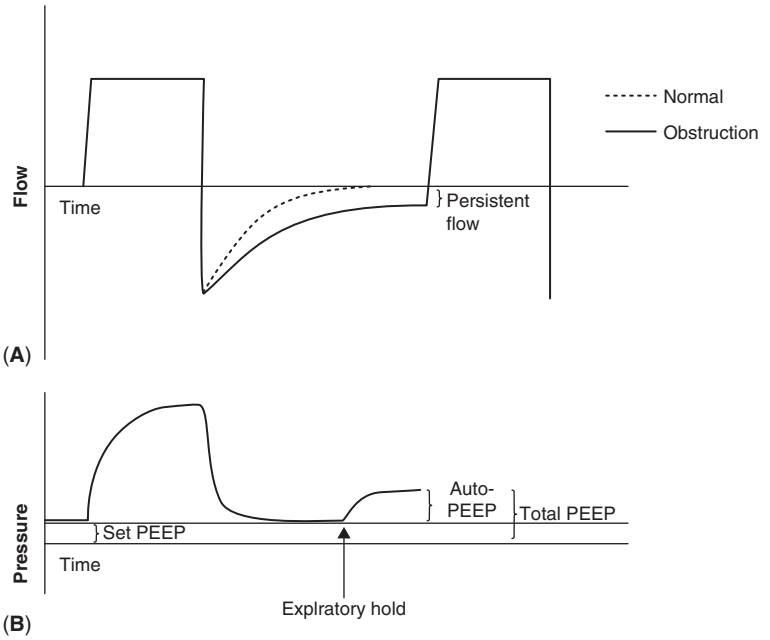

Figure 6.13 A. Persistence of end-expiratory flow in the setting of auto-positive end-expiratory pressure (auto-PEEP). Auto-PEEP is end-expiratory pressure above that generated by the ventilator and is secondary to inadequate expiratory time to empty the lungs before the next breath is delivered. Note that auto-PEEP generates persistent flow at the end of the timed exhalation rather than the normal return to zero well before the next inhalation. In panel B, an expiratory hold maneuver is applied by occluding the expiratory port. The pressure measured minus set PEEP is auto-PEEP. *Source*: From Ref. 8.

Table 6.32 Common Ventilator Modes

- Controlled mechanical ventilation (CMV)
- Assist control (AC)
- Synchronous intermittent mandatory ventilation (SIMV)
- Pressure support ventilation

Pressure support ventilation (PSV) is a patient-triggered, pressure-limited method that provides a pressure application for each patient-initiated breath. Flow is decelerating rather than constant and the initial increase in pressure is influenced by both the P_{res} and $P_{elastic}$ (Figs. 6.11 and 6.15) (8). As stated above, this can be added to SIMV. In pure PSV, the respiratory rate is determined by the patient and VT by the magnitude of constant pressure applied during inspiration as compared to respiratory compliance.

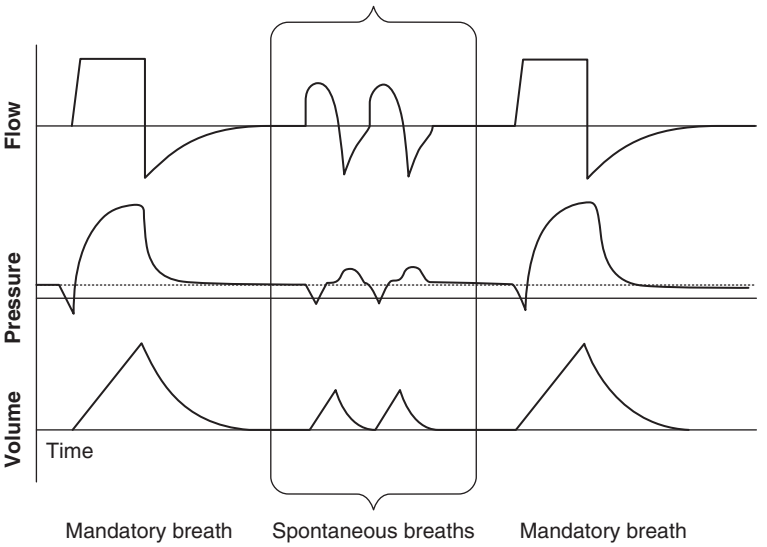

Figure 6.14 Synchronized intermittent mandatory ventilation mode. As in assist-control mode, mandatory breaths are patient triggered. However, breaths taken between mandatory breaths (bracketed) are not supported. The rate, flow, and volume are determined by the patient's strength, effort, and lung mechanics. *Source*: From Ref. 8.

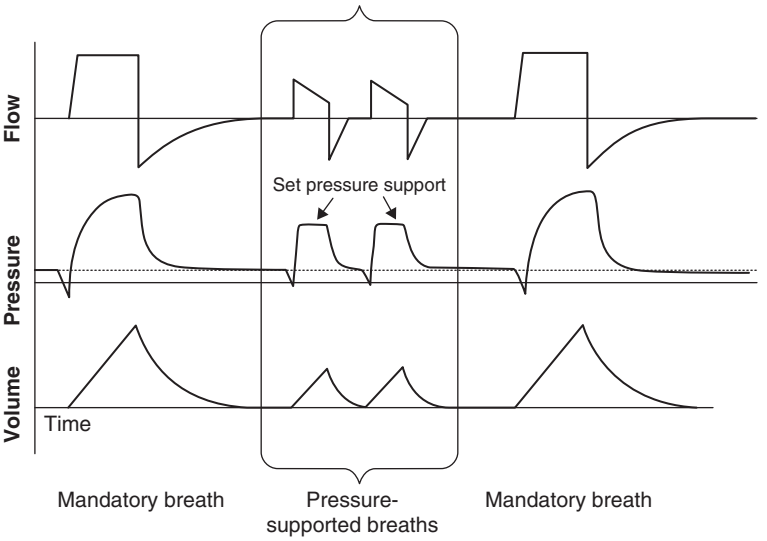

Figure 6.15 Synchronized intermittent mandatory ventilation (SIMV) with pressure support ventilation (SIMV+PSV) mode. The first and last tracings are identical to SIMV. During pressure-supported breaths (bracketed), the ventilator delivers a preset inspiratory pressure that is terminated when flow drops below a preset threshold. The breaths are patient triggered. *Source*: From Ref. 8.

Ventilator-Induced Lung Injury (Table 6.33)

While mechanical ventilator support can be life-saving, adverse effects from positive pressure application to the lungs and thorax have been documented for at least several decades. Lung damage from positive pressure ventilation has been variously labeled barotrauma and/or volutrauma, as investigations have attempted to discern whether sufficient pressure without marked alveolar distention or sufficient alveolar distention without a marked increase in pressure can cause such injury. More recently, this distinction has been subsumed into ventilator-induced lung injury (VILI) and much of current ventilator strategy attempts to diminish this threat.

As defined by Marini and Gattinoni, VILI…"is a complex process initiated by the repetitive application of excessive stress or strain to the lung's fibroskeleton, microvasculature, terminal airways, and delicate juxta-alveolar tissues."(113) This process can result in both local inflammatory cell activation and direct mechanical tissue damage, resulting in pathology similar to ALI and ARDS (114,115).

ALI and ARDS are characterized by non-homogenous lung pathology and, presumably, the less injured lung is more at risk for VILI. As described in more detail below, limiting elevations in transalveolar pressure [Ptrans = (Pplat − Ppl)] is a principal consideration for protecting the less damaged lung (113,116).

The primary mechanism of ventilator-induced circulatory disturbance is decreased venous return from an extraluminal increase in CVP and an increase in thoracic venous resistance (see chap. 3). This is most evident with high PEEP application, but the combined effect of positive-pressure ventilation and increased abdominal pressure can result in marked reductions in venous return even with PEEP at low levels (117–119). Less often, the increase in pulmonary vascular resistance from PEEP application can result in a right to left shunt through a patent foramen ovale and worsening arterial oxygenation (120).

VILI results in both local and systemic augmentation of proinflammatory mediator concentrations (115). In addition, decreased cardiac output can result in inadequate oxygen delivery. Therefore, positive-pressure ventilation can enhance both mechanisms of cellular threat during surgical critical illness.

"Protective" Ventilator Management

While lung protective ventilator management is directed at a single organ system, the ultimate potential benefit is improved patient survival. Therefore, the systemic effects of better ventilator management (decreased systemic inflammation, improved cardiac output) may have more importance than local organ protection. The use of a low VT (6 ml/kg of predicted body weight) and the associated permissive hypercapnia have resulted in patient protection for those with ALI and ARDS (121,122). These results serve as the underpinning for guidelines promoted for both surgical and medical patients (113,123).

More controversial is the addition of "high-PEEP" and lung recruitment tactics to the low VT strategy. PEEP can improve FRC, a physiologic volume characteristically decreased in ARDS, by opening collapsed airways and keeping them open. When FRC increases, lung compliance and oxygenation improve (124). However, the patchy nature of ALI and ARDS can result in "non-recruitable" lung, that is lung segments that are either already open and subject

Table 6.33 Ventilator Induced Injury

I. Ventilator-induced lung injury
A. Mechanical damage
B. Mediator stimulation
II. ventilator-induced circulation injury
A. Decreased venous return
B. Intracardiac shunt
III. Ventilator-induced systemic injury
A. Mediator circulation
B. Decreased oxygen delivery

Table 6.34 Less Common "Ventilator" Strategies

Esophageal pressure monitoring
Inhaled vasodilators
Prone positioning
High-frequency oscillation

to VILI, or units that are so diseased that increased pressure has no effect. Recruitment is characterized by a sustained increase in airway pressure (e.g., a plateau pressure of 45 cm H_2O) for a few minutes followed by an increase in PEEP. When recruitable lung is present, increased PEEP does improve aeration. Curiously, recruitable lung is linked to poorer oxygenation (PaO_2:FiO_2 <150) and compliance, suggesting that this management may be particularly useful in severe cases (125). In addition, when ARDS is compared to ALI, high PEEP (mean plateau pressure 29 cm H_2O) may result in a survival advantage as compared to lower PEEP (mean plateau pressure 23 cm H_2O) (126). Once again, worse lung disease may be linked to more recruitable lung units than that can respond to higher ventilator pressures. An improvement in oxygenation, carbon dioxide elimination, and compliance would support achievement of a therapeutic advantage as compared to enhanced lung injury risk (127).

Less Common "Ventilator" Strategies (Table 6.34)

VILI is presumably linked to excessive transalveolar pressure (Ptrans). Pleural pressure (Ppl) is influenced by both lung and chest wall compliance. Surgical critical illness includes many states that alter chest wall compliance, for example, chest trauma, increased abdominal pressure, and large volumes of fluid sequestration. Decreased chest wall compliance is associated with increased pleural pressure during positive-pressure ventilation. High ventilator pressures may not result in high transalveolar pressures when Ppl is elevated. Esophageal pressure (EP) measurement allows calculation of Ptrans and the adjustment of PEEP to maintain expiratory Ptrans in a "physiologic" range adjusted to the severity of poor oxygenation. Using such a strategy, one study showed improved oxygenation and lung compliance, as PEEP was most often applied at a higher level than in control patients. Despite the higher PEEP, plateau pressures at 72 hours were 28 cm H_2O in the EP group as compared to 25 in the controls. Importantly, Ptrans at end-inspiration was no different (116). The improvement in lung compliance suggests that patients who maintain a "physiologic" Ptrans following lung expansion and PEEP application define the group with recruitable lung segments.

Increased pulmonary vascular resistance and diminished perfusion to better ventilated lung segments is characteristic of ALI and ARDS (128). Improving the pulmonary blood flow to these better ventilated lung units would presumably decrease the physiologic shunt and VD alterations in these conditions. Attempts to use systemic vasodilators (i.e., nitroglycerin, nitroprusside, prostacyclin) were effective in reducing pulmonary vascular resistance, but caused two adverse effects: systemic hypotension and an increase in physiologic shunt (129,130). In contrast, inhaled vasodilators [nitric oxide (iNO) and prostacyclin (iP)] appeared to improve the perfusion to better ventilated lung units, thereby reducing both shunt and VD. Many investigations have studied the dosing and magnitude of the effect of these agents without any clear benefit documented. Both are effective in reducing pulmonary vascular resistance and, therefore, may be particularly useful for cardiovascular management. iP is less expensive than iNO, and this may prompt further interest in the use of this agent for "salvage" therapy in ARDS (128,129).

Prone ventilation is a strategy to improve V/Q distribution by gravitational effects. Experimental data suggest that the supine position is particularly detrimental following lung injury and that prone positioning improves aeration to the dorsal lung without decreasing perfusion (131). Human data are conflicting vis a vis a survival benefit from prone ventilation, but improvement in oxygenation is sufficiently common to consider prone ventilation as another "salvage" therapy for ARDS (113,132,133).

Table 6.35 Adjuncts to Ventilator Management

I.	Drainage of pleural fluid
II.	Neuromuscular blockade
III.	Avoidance of overfeeding
IV.	Early tracheostomy

High-frequency oscillatory ventilation (HFOV) has become the most common high-frequency ventilator technique used in ALI and ARDS. Small VTs (1–4 ml/kg) are delivered at a high frequency (3–15 Hz), with the oscillator mechanism allowing active expiration as well as inspiration. The principal variable that appears to improve oxygenation is a higher $\overline{P}aw$. Presumably, the smaller VTs result in a lung protective effect despite the higher mean airway pressure (134). A recent meta-analysis suggests that HFOV may provide a survival advantage despite only a modest improvement in PaO_2/FiO_2. Once again, HFOV appears sufficiently effective to be an alterative for the most severe cases of respiratory failure (135).

Adjuncts to Ventilator Management (Table 6.35)

While the advantages of therapeutic thoracentesis for surgical patients without critical illness may be meager, patients with surgical critical illness can demonstrate an improvement in oxygenation, oxygen delivery, and oxygen consumption following drainage of volumes from 300 to 2,980 ml (136).

Short term (48 hrs), early (within 48 hrs of onset) use of neuromuscular blockade for patients with ARDS and PaO_2/FiO_2 <150 was shown to reduce mortality at 28 days. Presumably, paralysis improves the function of the lung protective strategy by allowing better patient-ventilator synchronization (137).

Nutritional support is a part of management of surgical critical illness. However, while nutrition is essential and some nutritional strategies are particularly beneficial ("ALI/ARDS" and chap. 8), overfeeding can result in a metabolic and respiratory stress (138).

One of the most effective adjuncts to ventilator management is early tracheostomy (within 7 days of respiratory failure). The mechanical and access advantages of a tracheostomy result in more rapid weaning and shorter stays in the ICU. Therefore, this adjunct should be seriously considered in any respiratory failure patient expected to need a ventilator for more than a few days (139,140).

SUMMARY

Respiratory malfunction and/or failure are a common component of surgical critical illness. A firm understanding of the underlying pathophysiologic mechanisms of pulmonary compromise and principles of management of the lungs and ventilators allows the surgical critical care practitioner to implement diagnostic and therapeutic strategies that encompass the entire surgical critical illness, not just the pulmonary component. In particular, strategies that support sufficient arterial oxygenation yet promote a hyperdynamic, augmented oxygen delivery, and consumption state (i.e., achievement of the Flow Phase of shock) as well as strategies that limit the toxic effects of systemic inflammation are the cornerstones for effective surgical critical illness decision making for patients with respiratory compromise.

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7 | The renal system

BASIC PHYSIOLOGY

The kidneys help preserve intravascular volume, excrete products of metabolism, and regulate acid–base status. The physiology of sodium and water reabsorption that is linked to renal blood flow engages surgical critical care clinicians on a daily basis. Urine output is commonly used as a substitute for measurement of renal perfusion and as a surrogate for cardiac output monitoring. Acid–base disturbances are also a daily feature of surgical critical illness. Acute kidney injury (AKI) regularly accompanies shock from hypoperfusion and/or systemic inflammation. Avoidance of and/or limiting the duration of AKI is linked to the avoidance and/or limitation of shock and, therefore, is an important strategy to improve outcome in surgical critical illness.

Selected aspects of renal physiology provide the foundation for the concepts of evaluation and management of renal function that are pertinent to surgical critical illness.

Renal Circulation

The renal circulation has the following four components: outer cortex (75%), juxtamedullary cortex and outer medulla (20%), vasa recta and inner medulla, and perirenal and hilar fat (combined 5%). The high rate of outer cortical blood flow is ideal for glomerular filtration, the slow blood flow in the vasa recta helps maintain osmotic gradients in the peritubular space. During reduced renal blood flow, outer cortical perfusion is decreased and juxtamedullary cortical and outer medullary flow increases. This adjustment maintains blood flow where urinary concentration mechanisms are most active (1,2).

Glomerular Filtration

The first process in the formation of urine is glomerular capillary ultrafiltration of blood. This results in a fluid that is low in protein and contains all solutes not bound to non-filterable proteins.

GFR (the amount of blood filtered/minute) is measured by determining the clearance from the plasma of a substance that is filtered but neither secreted nor absorbed by the renal tubules. Dividing the amount excreted in the urine over a given amount of time by the plasma concentration of that substance in normal adult humans results in a GFR of 100–125 cm^3/min (144–160 L/day) (2).

GFR is influenced by a variety of mechanism that attempt to maintain filtration despite the potential of marked alterations in renal blood flow (Table 7.1) (3,4).

Tubular Reabsorption

The 100–125 cm^3/min of glomerular filtrate enters the proximal renal tubule, which, along with the rest of the tubular system, reabsorbs about 98% of the filtered water and solutes. The proximal convoluted tubule (PCT) reabsorbs approximately 60% of overall glomerular filtrate, with greater percentages of phosphate, water and bicarbonate (80%), and glucose and amino acids (100%). The thick ascending limb of Henle absorbs approximately 30% of the filtrate with the distal convoluted tubule responsible for about 7% and the collecting ducts absorb the remaining few percent (3,5).

Sodium Reabsorption

The reabsorption of sodium is the major active transport mechanism of the entire nephron. The three major determinants of sodium reabsorption are listed in Table 7.2. GFR influences the active process of sodium reabsorption in the proximal tubule, such that an increase in filtration is associated with an increase in total absorption (glomerular–tubular balance). This process appears to be independent of direct neurohumoral control (2,5).

Table 7.1 Regulation of Glomerular Filtration Rate

I. Autoregulation—constriction and dilation of afferent and efferent arterioles
A. Afferent dilation with hypotension—prostaglandins
B. Efferent constriction with hypotension—angiotensin II
II. Tubuloglomerular feedback
A. Chloride delivery to macula densa—increase in afferent arteriolar tone
B. Adenosine—afferent constriction
C. Thromboxane—afferent constriction
D. Prostaglandins—afferent dilation
E. Nitric oxide—afferent dilation
F. Norepinephrine—afferent and efferent constriction
G. Angiotensin II—efferent constriction
III. Other potential mediators of filtration regulation
A. Endothelin—potent vasoconstriction
B. Vasopressin—low dose has little effect
C. Atrial natriuretic peptide—afferent dilation, efferent constriction

Table 7.2 Determinants of Sodium Reabsorption

• Glomerular filtration—proximal tubular reabsorption—"glomerular tubular balance"
• Aldosterone
• Natriuretic factors
Atrial natriuretic peptide
B–type natriuretic peptide (brain natriuretic peptide)
Urodilatin

Proximal tubule absorption is augmented by adrenergic innervation and low-dose angiotensin as well as insulin and glucocorticoids. Dopamine inhibits proximal sodium absorption and this effect can by augmented by natriuretic hormones—atrial natriuretic peptide (ANP) and urodilatin (Urod) (5,6).

In the thick ascending loop of Henle, glucocorticoids, vasopressin, beta adrenergic stimulation, and insulin augment absorption, whereas dopamine, ANP, and Urod are inhibitory (5).

Aldosterone augments sodium absorption and is released as the end product of the renin-angiotensin-aldosterone hormonal axis. Renin is released from the juxtaglomerular cells of the kidney as a response to diminished renal perfusion, diminished sodium supply to the distal tubule, and beta adrenergic stimulation. Renin converts renin substrate (produced in the liver) into angiotensin I, which is converted mostly in the lungs into angiotensin II, a potent arteriolar vasoconstrictor and a stimulus for aldosterone release from the adrenal glands. Aldosterone production is also augmented by hyperkalemia, adrenocorticotropic hormone (ACTH) elevation, and hyponatremia (7).

To maintain electroneutrality in the tubular lumen, potassium and hydrogen ions are exchanged for sodium. Hydrogen ion exchange results in increased intracellular bicarbonate. The secreted hydrogen ions react with luminal bicarbonate and reduce bicarbonate concentration in the lumen. Both intracellular and intraluminal reactions of hydrogen ions and bicarbonate are facilitated by carbonic anhydrase. In the distal tubule, hydrogen ion secretion continues, especially when sodium absorption is high (aldosterone secretion). To preserve anion electroneutrality, either chloride or bicarbonate must accompany sodium. During states of chloride deficiency or strong sodium reabsorption (e.g., hypoperfusion of the kidneys, loss of chloride from the stomach, elevated aldosterone or cortisol levels, diuretics), sodium-hydrogen exchange is augmented and results in increased bicarbonate absorption (or intracellular production) and excretion of hydrogen in the face of a metabolic alkalosis (paradoxical aciduria) (2,8,9).

Table 7.3 Definition of Acute Kidney Injury

An abrupt reduction (within 48 hrs) in kidney function
Increase in creatinine ≥0.3 mg/dl
Percentage creatinine increase ≥50%
Oliguria (<0.5 ml/kg/hr) for >6 hrs

Stages	Creatinine	Urine output
1	Increase ≥0.3 mg/dl Increase <2.0 × baseline	<0.5 ml/kg/hr >6 hrs
2	Increase >2.0 <3.0 × baseline	<0.5 ml/kg/hr >12 hrs
3	Increase >3.0 × baseline Creatinine >4 mg/dl Need for RRT	<0.3 ml/kg/hr >24 hrs

ANP is a potent inhibitor of sodium reabsorption that is released from the atria in response to an increase in atrial stretch. Urodilatin is a pro-ANP fragment that is produced in the kidney and is increased during volume expansion. B-type natriuretic peptide (BNP—previously termed brain natriuretic factor) is principally released from the cardiac ventricles, and some from the brain. BNP concentrations can exceed ANP blood levels during heart failure and in various other critical illnesses (10,11).

Water Reabsorption

Water reabsorption is an osmotically driven, passive process that follows sodium migration from the tubular lumen to the interstitial space. However, in the medullary interstitium, sodium is absorbed without water in the ascending loop of Henle. The shape of the loop allows for a progressive increase in interstitial osmolality near the tip of the loop (counter-current mechanism) that can be augmented by vasopressin-induced urea absorption.

In the collecting duct, vasopressin increases water absorption via the V2 receptor that increases the action of pre-formed water channels called aquaporin-2. Water migration through these channels can result in a urine osmolality approaching 1,200 mOsm, the medullary concentration produced by the counter-current mechanism (3).

Vasopressin secretion is primarily regulated by serum osmolality and the adequacy of systemic perfusion. Inadequate perfusion is a more potent stimulus than osmolar regulation such that hyponatremia can develop as a consequence of circulatory deficits (12).

Monitoring of Renal Function

The common clinical parameters used to monitor renal function are rate of urine flow and blood urea nitrogen (BUN) and serum creatinine (CR). Too little urine output (oliguria) for the adult is defined as $<0.5\,cm^3/kg/hr$. An increase in BUN and/or CR serves to indicate decreasing glomerular filtration.

Acute Kidney Injury

AKI is defined by the criteria listed in Table 7.3. AKI, like shorter durations of oliguria, can be secondary to pre-renal, intrinsic renal, or post-renal etiologies (Table 7.4). For hospitalized patients who develop kidney malfunction, the most common intrinsic renal insult is cataloged under the term acute tubular necrosis (ATN), even when anatomical tubular injury is minimal (*vide infra*), and the most common post-renal cause is a blocked urinary catheter (rare).

History and Physical Examination

The first step in evaluating the etiology of oliguria and/or an increase in BUN and CR is reviewing history and physical examination information, the most pertinent of which are listed

Table 7.4 Etiologies of Oliguria and Acute Kidney Injury in Hospitalized Patients

I. Pre-renal
A. Hypovolemic hypoperfusion
B. Cardiogenic hypoperfusion
II. Renal
A. ATN (Misnomer)
B. Interstitial nephritis (very rare)
III. Post-renal
A. Blocked catheter
B. Bladder obstruction

Table 7.5 Pertinent History and Physical Exam Information for Oliguria or Acute Kidney Injury

1. History
• Hypoperfusion
• Operation
• Renal toxic drugs
• Pre-existing renal disease
• Severe inflammation
Diuretics
Osmolar agents
2. Physical examination
• Blood pressure
• Pulse
• Temperature
• Mentation
• Skin color and temperature
• Percussion/palpation of bladder
• Exam of prostate

in Table 7.5. Most of this information addresses the state of global circulation prior to and during the onset of a renal threat as well as the presence or absence of renal toxins or bladder obstruction (see chap. 3 for more about accurate hemodynamic diagnoses).

The drugs used most commonly that directly influence urine output are diuretics, which either work as a filtered osmotic load (e.g., mannitol, intravenous contrast) or interrupt sodium reabsorption (e.g., furosemide, hydrochlorothiazide). In either case, more sodium and water are excreted than otherwise, with a urine sodium concentration of 30–70 Meq/L, resulting in the loss of more water than sodium.

Laboratory Investigation

Urine Osmolality and Specific Gravity

Low urine output secondary to renal hypoperfusion is the normal physiological response to decreased glomerular perfusion and augmented sodium and water reabsorption. Secretion of vasopressin allows tubular reabsorption of water that will increase urine osmolality above plasma levels (i.e., >290 mOsm/L) and results in specific gravity (SG) greater than that of plasma (>1.010, but usually <1.030). Unfortunately, osmolality and SG can be increased by other mechanisms, especially the excretion of osmotically active substances like glucose and and intravenous and/or arterial contrast, which not only increase SG but often promote diuresis. Diuresis with increased SG (especially when >1.030) is a clue that a large, osmotically active molecule is in the urine. A physiologic diuresis secondary to well maintained intravascular volume would more likely decrease SG. After such stress as surgery, trauma, or severe infection, the most likely cause of a large urine output with elevated SG is excretion of glucose secondary

to increased blood glucose from the metabolic response to tissue injury. A urine sugar level will rapidly determine if such is the case.

Urine Electrolytes and Creatinine

With oliguria secondary to hypoperfusion, the augmented sodium reabsorption mechanisms typically result in urine sodium concentrations <20 Meq/L. When urine sodium is >40 Meq/L, the inference is that the renal tubules are injured and cannot respond to aldosterone. The low urine sodium of aldosterone effect is usually associated with a higher urine potassium (>30 Meq/L) even when hypokalemia is present.

Osmotic substances in the urine that result in retention of intraluminal water can limit the magnitude of sodium reabsorption. Usually, however, such a potential effect can be elucidated by measuring the SG. As stated above, a SG >1.030 is suggestive of a non-physiologic osmotic effect on urine chemistries.

The fractional excretion of sodium (FE_{Na}), the percent of filtered sodium that is excreted, is considered a more accurate indication of renal hypoperfusion versus poorly functioning tubules.

$$FE_{Na}(\text{percent}) = \frac{\text{urine sodium} \times \text{plasma creatinine}}{\text{plasma sodium} \times \text{urine creatinine}} \times 100$$

Values <1.0% are consistent with hypoperfusion; values >2% are most consistent with tubular malfunction. However, several reports have demonstrated FE_{Na} values <1% in patients with a clinical course more consistent with tubular damage. This is seen most often in patients with intense stimuli for sodium reabsorption (e.g., congestive heart failure, cirrhosis, burns) or particular etiologies of renal damage (e.g., acute glomerular and interstitial nephritis) (4,13). In addition, confounders such as loop diuretics and osmotic substances in the urine might increase urine sodium concentrations and the calculated FE_{Na} despite the presence of a pre-renal state.

BUN and Serum Creatinine

BUN and creatinine levels are easily obtained estimates of glomerular filtration. Urea is a product of liver protein metabolism and can be influenced by the amount of protein administered or the metabolic capability of the liver. A diet deficient in protein coupled with a damaged liver may result in a low BUN despite reduced glomerular filtration. High protein intake with good liver function might produce the opposite effect. Creatinine is the end product of creatinine metabolism in muscle and is relatively constant from day to day. Except with little (e.g., older, wasted patient) or excessive muscle breakdown (rhabdomyolysis), creatinine ranges from 0.6 to 1.0 mg/100 ml in females, and 0.8 to 1.3 mg/100 ml in males with normal glomerular filtration (3).

For every 50% reduction in glomerular filtration, serum creatinine doubles (Fig. 7.1). Therefore, when normal function precedes an insult small increments in creatinine represent relatively large reductions in glomerular filtration. Subsequently, similar increments in creatinine do not indicate the same percentage loss of function. For instance an increase in creatinine from 1.0 to 2.0 mg/dl represents a larger percentage decrease in glomerular filtration than a subsequent increase from 2.0 to 3.0 mg/dl (14).

After filtration, BUN is also reabsorbed. In oliguric states with preserved tubular function (hypoperfusion), BUN will typically increase more than creatinine and elevate the normal BUN/CR ratio of 10–15 to 20–50 range. Therefore, calculation of the BUN/CR ratio can assist the recognition of hypoperfusion/pre-renal states (4).

Urinalysis

Urinalysis is particularly useful for determining SG, the presence of glucose, and for evidence of tubular damage (tubular casts) as well as acute glomerular or interstitial alterations (protein, red cell casts, eosinophils) (4).

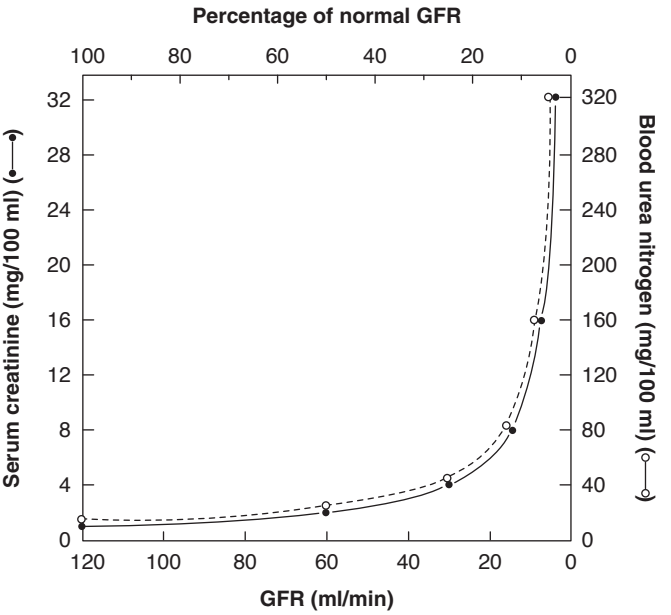

Figure 7.1 Graphic representation of the increase in creatinine as glomerular filtration rate (GFR) decreases. Once GFR is approximately 30% of normal, small reductions in GFR may result in marked creatinine elevation. *Source*: From Ref. 14.

Pathophysiology of AKI

Hypoperfusion

Hypoperfusion secondary to hypovolemia (hypovolemic hypoperfusion) or cardiac malfunction (cardiogenic hypoperfusion) is the etiology of pre-renal oliguria and pre-renal AKI. Global hypoperfusion from either etiology and the associated reduction in glomerular filtration result in similar systemic and renal neuroendocrine activation that cause sodium and water retention from still functioning renal tubular cells. Stating this more simply—the kidneys cannot distinguish etiologies of hypoperfusion (6,12,15).

If the pre-renal state is short lived (usually no more than a few hours), no anatomical or severe physiological injury to the kidneys occurs and complete recovery follows restoration of adequate renal perfusion. If hypoperfusion persists, even in the absence of hypotension, then anatomical and/or severe physiological renal injury can follow, meeting the clinical definition of ATN. Ischemia of this magnitude incites an intra-renal inflammatory response (hypoperfusion begets inflammation) that contributes to cellular injury.

Despite this common description of ATN as the consequence of severe renal ischemia, usually there is a paucity of actual cell necrosis. Most renal cells are viable and some apoptotic rather than necrotic (4).

Inflammation

Ischemia–reperfusion, severe systemic inflammation, and nephrotoxin models of AKI are all associated with marked renal inflammation. Damage to renal endothelial and/or tubular cells can initiate a potent local inflammatory response that is augmented by autocrine and paracrine processes (16).

Severe systemic inflammation is now considered the primary etiology of AKI, and like ischemic AKI, is associated with little anatomical evidence of necrosis (17–19). Instead, injured renal cells release damage-associated molecular patterns (DAMPs) (see chap. 4) that stimulate dedifferentiation of renal tubular epithelial cells to non-functioning units. Transforming growth factor beta (TGF-β) appears to be an important modulator of this dedifferentiation that can eventually be reversed, resulting in complete recovery (18).

Epidemiology of AKI

Reports of an AKI frequency of 20% in hospitalized patients and more than 50% in intensive care unit populations attest to how regularly the kidneys suffer during acute illness (20). Regardless of etiology, the occurrence of AKI during hospitalization is associated with increased mortality, even when the creatinine increase is as low as 0.3 mg/dl. As might be expected, mortality risk increases with further creatinine elevation and especially when renal replacement therapy is necessary (Table 7.3) (4,21–27).

Hemodynamic Management of AKI

Pre-renal oliguria is managed by reversing global hypoperfusion. This requires determining the specific etiology of hypoperfusion and providing appropriate therapy (see chap. 3). The epidemiologic data that link and increase in creatinine to higher mortality do not distinguish between creatinine elevation that is a result of disease versus a result of provider management. Therefore, it is possible that provider-induced renal insult (e.g., depletion of plasma volume with diuresis, administration of renal toxins, inadequate fluid administration) is as detrimental as disease-induced alterations.

For surgical patients, hemodynamic "optimization" using cardiac output measurement and monitors of oxygen utilization is associated with reduced AKI, even when this effort is provided in the post-operative time frame (28). This finding infers a direct link between provider attention to circulation deficits and the threat of kidney injury. Goal-directed hemodynamic therapy for severe systemic inflammation is also associated with improved renal function (19).

Once intrinsic renal damage is in place, it is difficult to correlate specific deficits in renal function with renal blood flow, per se (20). That is, the creatinine might continue to increase despite excellent renal blood flow. However, it is also difficult to presume that injured kidneys benefit from new and/or additional episodes of hypoperfusion. In fact, increasing renal perfusion, usually by attention to global perfusion deficits, may result in more urine output and avoidance of renal replacement, despite further creatinine elevation.

Therefore, the identification and management of inadequate cardiac output is a principal therapeutic concept for renal preservation, just as it is a principal concept for improving patient survival. Since urine output from intrinsically injured kidneys will no longer serve as a practical monitor of global circulation, precise hemodynamic analysis will often demand the use of echocardiograms and invasive monitoring. Patients with AKI should not be maintained in the Ebb phase of shock because of the fear of the effects of resuscitation. Neither the kidneys nor the patient will survive unless the Flow phase is sought and achieved.

Finally, the avoidance of drugs that can alter glomerular blood flow (non-steroidal anti-inflammatory agents/analgesics, angiotensin-converting-enzyme inhibitors) is an adjunctive strategy (29).

Management of Inflammation in AKI

The management of systemic inflammation that can cause AKI is described in the chapter 4. At present, there are no renal-specific anti-inflammatory management strategies, save for attention to the type of dialysis membrane used when hemodialysis is used for renal replacement in severe AKI. The use of a "biocompatible" dialysis membrane that presumably causes less complement activation is associated with improved renal recovery (30).

Inflammation is a principal mechanism for nephrotoxin renal injury. Avoidance of renal toxins is a fundamental strategy in AKI unless toxin administration is unavoidable for optimum management of the patient (e.g., intravenous contrast for suspected pulmonary embolism) (4).

Rhabdomyolysis results in a toxic injury to the kidneys that is also associated with systemic inflammation that is either a consequence of the muscle injury itself (e.g., crush injury to an extremity) or secondary to another inflammatory process (e.g., pancreatitis). Myoglobin can cause both ischemic renal insults and tubular obstruction. Ischemia-reperfusion-induced

inflammation can then follow the initial ischemic process (31,32). While the infusion of bicarbonate and the osmotic diuretic mannitol have been recommended to protect renal tissue from myoglobin toxicity, there is little data supporting the effect of this management strategy. As with other etiologies of AKI, an excellent cardiac output is the most effective therapeutic goal (31).

Additional Management Concepts for AKI

Utilization of loop diuretics does not result in improved recovery of renal function, although it may result in less need for dialysis. One study concluded that loop diuretics were associated with increased mortality and non-recovery of renal function (33,34).

Which fluid to use for plasma volume expansion has been studied, suggesting that crystalloid as compared to synthetic colloids is associated with less frequent AKI (35).

Cardiac surgery patients who develop AKI appear to respond favorably to the infusion of recombinant human atrial natriuretic peptide (hANP) with less need for renal replacement (36). The perioperative use of hANP in patients undergoing abdominal aortic aneurysm repair resulted in improved renal function (37).

The infusion of alkaline phosphatase and the resultant inhibition of nitric oxide production in the kidneys have been shown to improve sepsis-associated AKI in humans (38).

Renal Replacement Techniques: Continuous Hemofiltration and Dialysis

The relative indications for renal replacement in AKI are listed in Table 7.6 and the methods used in Table 7.7. As emphasized in the chapters 3 and 4, total body sodium and water excess does not guarantee increased intravascular volume. However, when truly excessive, increased vascular volume may be removed with renal replacement techniques (especially continuous methods) and potentially improve cardiac function. In such patients, renal replacement may also assist nutritional therapy, allowing several liters of intravenous or intestinal food to be administered. Metabolic acidosis and hyperkalemia are effectively treated by renal replacement, but phosphate filtration is less effective with dialysis as compared to continous techniques. "Uremia" is an ill-defined syndrome that may include altered mental status, pleural/pericardial effusions and coagulopathy. Uremia is associated with blood urea levels close to 100 mg/dl. Certain toxins (antibiotics, salicylates) may be removed only by renal replacement.

Hemodialysis (usually over 3–4 hours) is the most common method used in chronic renal failure and is used frequently in AKI. Hemodialysis in surgical critical illness is often accompanied by hemodynamic instability resulting in administration of fluids and/or drugs to maintain cardiac output. In addition, worsening hypoxemia may be noted. The etiology of these alterations is unclear, but may relate to pulmonary and/or systemic vasodilation in the setting

Table 7.6 Indications for Renal Replacement

1. Metabolic acidosis
2. Hyperkalemia
3. Uremia
4. Toxin removal
5. Congestive heart failure
6. Aggressive nutritional support

Table 7.7 Renal Replacement Methods

1. Continuous veno-venous hemofiltration
2. Hemodialysis
3. Peritoneal dialysis

of normal or low intravascular volume. In one report, daily hemodialysis that removed about two-thirds less ultrafiltration volume as compared to every-other-day hemodialysis was associated with less frequent hypotension, better control of uremia, more recovery of renal function, and lower mortality (39).

The development of biocompatible "high flux" synthetic membranes with greater permeability than conventional hemodialysis membranes made the development of continuous renal replacement therapy (CRRT) possible in the late 1970s. The addition of a pump into the circuit allowed continuous veno-venous hemodiafiltration (CVVH) and permitted the application of hemofiltration in patients with a narrow arteriovenous pressure gradient.

Peritoneal dialysis via insertion of a catheter into the abdominal cavity is a slower, continuous method of dialysis that does not require vascular access and results in less hemodynamic variation. This approach is rarely used in surgical critical illness.

Solute clearance using RRT may be either convective (filtration) or diffusive (dialysis). If ultrafiltration (CVVH) is used, excess fluid and electrolyte losses must be replaced. Fluid flux may be impressive: more than a liter per hour is not unusual. Sodium, bicarbonate, calcium, phosphate, and magnesium replacement require special attention and all electrolytes require careful monitoring (40). In addition, therapeutic drugs can be cleared by ultrafiltration often demanding measurement of blood levels and collaboration with a pharmacist to ensure effective concentrations.

When dialysis is the predominant form of solute clearance, the composition of the dialysate can make electrolyte balance easier to control. The semipermeable dialysis membrane permits diffusion of solute in both directions. A steady state is eventually approached. Transmembrane pressure differences drive fluid movement but solute clearance depends on the size of the pores in the filter membrane. Molecules smaller than 3,000 Dalton pass readily and drugs of this size are filtered, including vasoactive amines and antibiotics. Again, close pharmacokinetic monitoring is necessary to ensure proper therapeutic dosing. (41).

CRRT methods allow for removal of higher molecular weight molecules (up to 20,000 Dalton), some the size of inflammatory mediators. Hope that clearance of inflammatory mediators might decrease the magnitude of systemic inflammation and improve survival and/or renal recovery has not been supported in clinical research, even when "high-dose" or "higher-intensity" filtration regimens are used (40,42,43).

CRRT permits full nutritional support including full protein repletion even in severe catabolic states. Amino acids are filtered in a flow-dependent manner, typically 10% of the administered solution. Nitrogen balance studies, including the nitrogen removed in the effluent fluid (FUN) as well as any excreted urinary urea nitrogen (UUN), can guide the nutrition support plan.

FLUID AND ELECTROLYTES AND SELECTED METABOLIC PROBLEMS

Body Fluid Compartments

With the introduction of radioactive isotopes around the time of World War II, the measurement of body fluid spaces and electrolytes became scientifically more exact. Tables 7.8 and 7.9 are listings of the water spaces in the body as percent body weight (44). A similar table of the total electrolyte composition of the body is not clinically useful, except for the recognition that the sodium ion is predominantly extracellular and potassium ion predominantly intracellular. This allows the sodium ion to be used for a measure of the extracellular fluid space and the potassium ion to be used as a measure of the intracellular fluid space that has been termed the body cell mass. The body cell mass corresponds to functioning cells and has been shown to correlate well with definitions of malnutrition and response to nutritional therapy (45,46).

Fluid Therapy

Reasons for Fluid Administration

The primary reason why fluids are administered is to maintain intravascular volume and, thereby, promote a good circulation. As mentioned in the chapters 2–4, establishing a good-to-excellent circulation is key to successful outcomes in surgical critical illness. Therefore, as is

Table 7.8 Total Body Water as Percent Body Weight

Sex	Age	Percent
Male	16–30	58.9
Male	31–60	54.7
Male	61–90	51.6
Female	16–30	50.9
Female	31–90	45.2

Table 7.9 Distribution of Total Body Water as Percent of Body Weight

Sex	ICF	Total ECF	Plasma
Male	30.9	23.6	4.2
Female	25.9	22.7	4.2

Abbreviations: ICF, intracellular fluid; ECF, extracellular fluid.

described below, recognition and management of fluid alterations depends largely on the diagnostic and therapeutic principles related to the circulation.

In addition, fluid and electrolyte therapy is directed at correcting specific acid/base and electrolyte disorders. Often these disorders are linked to circulation deficits that must be corrected if the fluid/electrolyte therapy is to be successful.

A Basic Approach

The approach outlined below is designed to provide a simple method of determining the fluid and electrolyte requirements of most surgical patients. It is based on the concept that the unstressed patient lying in bed requires a baseline amount of water, sodium, and potassium to provide an adequate intravascular volume and electrolytes for normal urine output, sweating, and insensible loss. To this are added losses such as measured losses, which are usually external, and unmeasured losses, which are usually internal but still threaten blood volume.

Once these three components are estimated, the total fluid and electrolyte needs of the patient for a 24-hour period can be estimated. Table 7.10 is a description of this method.

Table 7.11 lists the sodium, water, and potassium requirements for a patient lying unstressed in bed. In general, water requirements decrease as age increases. There is an obligatory loss of potassium in the urine. Sodium loss is both by urine and sweating. Baseline water is required for insensible loss and to provide an adequate volume for urinary excretion of metabolites without depletion of plasma volume.

The most common losses measured are those of gastrointestinal secretions, with gastric losses the most frequent of these. Table 7.12 lists the average electrolytes of intestinal secretions. Upward of 10 liters a day of total secretions are produced by the intestinal tract with no more than 100–200 cm^3 excreted in the stool. Common volumes to encounter from gastric secretions are 1,000–1,500 cm^3/day. Newly formed distal ileostomies also frequently drain 1,000–1,500 cm^3/day (44).

Table 7.13 lists the electrolytes of intravenous fluids. A liter of 5% dextrose (D5) + half-normal (0.45%) saline has the equivalent of the baseline sodium requirements (5% dextrose has an osmolality close to plasma and may be administered without electrolytes to provide water. It is added to avoid hypo-osmolality when the sodium concentration is low and hypotonic). Two liters of D5 + quarter-normal (0.25%) saline have not only the baseline sodium requirements, but also the baseline water requirements of a 70-kg patient. If 20 Meq of potassium is added to each liter of D5 + quarter-normal saline, then we have 2,000 cm^3 of fluid containing about 77 Meq of sodium and 40 Meq of potassium. This closely approximates the baseline water, sodium and potassium needs of this 70-kg individual.

Table 7.10 Outline of Determination of Fluid and Electrolyte Requirements

- Determine baseline requirements
- Add measured losses and replace with appropriate solution
- Estimate unmeasured losses from the vascular volume and replace accordingly

Table 7.11 Baseline Sodium, Water, and Potassium Requirements

H_2O	25–30 cm^3/kg
Na^+	75 Meq
K^+	40 Meq

Table 7.12 Electrolytes of Gastrointestinal Secretions (Mean Values)

Source	Na^+ Meq/L	K^+ Meq/L	Cl Meq/L	HCO_3 Meq/L
Saliva	60	20	16	50
Gastric	59	9.3	89	0–1
Upper SB	105	5.6	99	10
Lower SB	112	5.0	106	15–20
Bile	145	5.2	100	50
Pancreas	142	4.6	77	70

Table 7.13 Electrolytes of Intravenous Fluids Meq/L

Solution	Na^+	K^+	Ca^{++}	Cl^-	HCO_3^-
Ringer's	130	4	2.7	109	28
NS	154			154	
1/2 NS	77			77	
1/4 NS	38.5			38.5	

The next task is to add to this the measured losses, depending on the site of the loss. Since the most common loss is that of gastric secretions with the predominant electrolyte being chloride, it can be seen by Tables 7.12 and 7.13 that a liter of D5 + half-normal saline with 40 Meq of KCl/L will provide well for the sodium, chloride, and potassium loss. Therefore, if our hypothetical patient lost one liter of gastric secretions, his intravenous fluids for the day might read 2,000 cm^3 of D5 + quarter-normal saline with 20 KCl/L plus 1,000 D5 + 0.45 saline with 40 KCl/L.

A much harder estimate is that of internal losses that threaten blood volume (Table 7.14). Obviously, bleeding is such a threat, but the most common fluid sequestration seen in general surgery is related to tissue injury and the dysfunction of the GIT that follows. Whenever tissues are injured, either by disease or by surgery, bleeding, and fluid exudation occurs. Following severe tissue injury and/or infection systemic inflammation ensues, resulting in a total body increase in capillary permeability. The fluid that exudes into the interstitium has the electrolytes of plasma, both at the local tissue injury site and in the rest of the body where there is increased capillary permeability. The small bowel, when irritated enough to produce an ileus, will become distended with fluid that also, on average, has electrolytes close to that of plasma. In addition, the bowel wall becomes edematous with plasma-like fluid. Interruption of cell membrane function during shock allows interstitial fluid to migrate into the intracellular space. Once again, since interstitial fluid has the electrolytes of plasma, this "loss" and threat to plasma volume includes plasma electrolytes.

Internal losses (commonly termed third space losses), that is, the fluid sequestration secondary to tissue injury and/or infection, usually consists of fluids with the electrolytes

Table 7.14 Etiologies of "Third Space" Losses Most Often Threats to Plasma Volume

- Area of tissue injury
- Total body increased capillary permeability
- GI lumen and GI wall
- Intracellular migration

of plasma. For this reason, intravenous solutions with electrolytes similar to plasma will most closely simulate the osmolality of the physiologic deficits.

Tissue injury and circulation deficits result in augmented vasopressin secretion. Under these circumstances hypotonic solution administration will result in hyponatremia and less expansion of plasma volume per cubic centimeter of fluid provided. This understanding is most vigorously supported by repetitive human investigations that demonstrate that hypertonic saline administration restores plasma volume with less water administration. Therefore, the amount of sodium provided is the principal determinant of expansion of extracellular fluid and plasma volume (47).

Monitoring Fluid Therapy

The first and foremost method for monitoring fluid therapy is to monitor the circulation as described in the chapter 3. In essence, therefore, a patient with recent major tissue injury and/or infection should receive intravenous fluids with electrolytes similar to that of plasma until the fluid sequestration phase has been completed and concerns about maintaining intravascular volume and a good circulation are less pressing (the use of hypertonic saline solutions for circulation resuscitation is discussed in chap. 4).

Depending upon the nature of the insult (e.g., elective colectomy for carcinoma as compared to emergency total colectomy for ischemic bowel) the magnitude and duration of the fluid sequestration phase can differ. In general, as Ranson demonstrated for pancreatitis in 1976, the more severe the threat the larger the magnitude of sequestration (48). Duration will depend on how quickly the underlying process subsides, often a difficult clinical prediction. Therefore, there is no arbitrary time limit for isotonic crystalloid administration. Instead, clinical analysis includes the daily assessment of the state of the fluid sequestration process while the goal of achieving an excellent circulation persists. The resolution of sequestration physiology is commonly evidenced by an increase in urine output accompanied by clinical information consistent with a hyperdynamic circulation (the Flow phase of shock).

Subsequent to the fluid sequestration phase, the concept of baseline fluid requirements plus replacing measured losses will usually suffice to maintain adequate fluid and electrolyte balance as well as a good circulation in patients who cannot spontaneously ingest these materials. This will not work well in cases where internal losses continue or in which excessive volumes of external losses are produced and cannot be measured easily. Under these circumstances, obtaining input and output measurements, obtaining serum electrolyte levels, and determining the concentrations of electrolytes in fluids lost from the body are all helpful. For instance, when measured losses are large (i.e., 3,000 cm^3 of gastric losses), aliquots of the solutions drained can be sent for electrolyte determinations to help prepare fluid and electrolyte therapy.

Acid–Base Physiology

The hydrogen ion concentration in body fluids is proportional to the distribution of buffer bases and the concentration of base to acid. This is described in the Henderson equation where the HCO_3 is the bicarbonate level. Since the carbonic acid level is proportionate to the dissolved carbon dioxide in the blood, the Henderson equation may be expressed as the second figure in Table 7.15. pH is the negative log of the concentration of hydrogen and is expressed as the Henderson-Hasselbalch equation in Table 7.15 (44).

Table 7.15 Acid–Base Equations

1. Henderson Equation	2. Henderson–Hasselbalch Equation
$[H^+] = \frac{K\,[H_2CO_3]}{[HCO_3]}$	$pH = \frac{PK + L\,OG[HCO_3]}{[H_2CO_3]}$
$[H^+] = \frac{24 \times PCO_2}{[HCO_3]}$	

Table 7.16 Relationship Between H^+ Concentration and pH

For pH range 7.10–7.50
pH 7.40 = $[H^+]$ of 40 mm/L
*Each change of [**H⁺**] of one mm/L = inverse change in pH of 0.01 pH unit*
pH 7.38 = 42 mm/L $[H^+]$
pH 7.39 = 41 mm/L $[H^+]$
pH 7.40 = 40 mm/L $[H^+]$
pH 7.41 = 39 mm/L $[H^+]$

Table 7.17 Normal Compensatory Adjustments in Acid–Base Disturbances

1. Acute respiratory acidosis
   $\Delta[H^+] = 0.8 \times \Delta\, pCO_2$
2. Chronic respiratory acidosis
   $\Delta[H^+] = 0.3 \times \Delta\, pCO_2$
3. Acute respiratory alkalosis
   $\Delta\,[H^+] = 0.8 \times \Delta\, pCO_2$
4. Chronic respiratory alkalosis
   $\Delta[H^+] = 0.17 \times \Delta pCO_2$
5. Metabolic acidosis
   $1.1\ \Delta[HCO_5] = \Delta\, pCO_2$
6. Metabolic alkalosis
   variable response, no formula available

An interesting empiric correlation between hydrogen ion concentration and pH has been found (Table 7.16). This means that for a large physiologic pH range, the change in pH associated with a change in hydrogen ion concentration is almost linear. This allows for determination of the status of a patient's acid–base condition by looking at the pH and pCO_2.

As listed in Table 7.17, for instance, acute respiratory acidosis should cause a change in hydrogen ion concentration of 0.8 × the change in pCO_2. Thus, a corresponding pH drop should follow. That is, if the change in pCO_2 is 10 mm Hg, then the change in hydrogen ion concentration would be 8 µmol. This should cause a normal pH of 7.40 to drop to 7.32. If presented with such a patient with a pH of 7.25, one would assume that under those circumstances that both a respiratory and a metabolic acidosis were present. Table 7.17 continues showing the expected changes in hydrogen ion concentration from a chronic respiratory acidosis, acute respiratory alkalosis, and chronic respiratory alkalosis. In addition, there is the expected drop in pCO_2 for each 1.1 Meq change in bicarbonate level during a metabolic acidosis.

From an understanding of these numbers, it is possible to determine whether a patient has a pure type of acid–base abnormality or a combined type. This becomes especially important in patients on the respirator, where the pCO_2 value may be independent of other acid–base phenomena (49).

Metabolic Acidosis

Table 7.18 lists the common etiologies of metabolic acidosis. The initial evaluation of metabolic acidosis requires calculation of the apparent anion gap as shown. More recently, this calculation has been augmented by calculation of the strong ion gap (SIG) that accounts for the effect of weak acids, mostly albumin, that can be altered in surgical critical illness (Table 7.19) (50).

The initial evaluation then follows by breaking up the etiologies of metabolic acidosis into those groups that produce an increase in the anion gap and those that do not. The most common cause of anion gap metabolic acidosis seen in surgical critical illness is lactic acidosis, and this etiology is associated with the highest mortality risk (50). As stated in the chapters 3 and 4, an elevated lactic acid can be secondary to either a deficit in the circulation and/or severe inflammation and the magnitude of elevation correlates with the severity of shock.

An increase in SIG without an elevated lactic acid is also associated with increased mortality risk, possibly linked to elevated blood phosphate concentrations (50).

The most common cause of a non-anion gap metabolic acidosis is the administration of high concentration chloride containing solutions, usually 0.9% NaCl that has a sodium and chloride concentration of 154 Meq/L (51). Whether or not hyperchloremic non-anion gap acidosis is detrimental is controversial, especially if an increase in serum chloride concentrations can result from disease as well as iatrogenic mechanisms (50,52).

The treatment of metabolic acidosis is to treat the underlying cause, that is, treat shock, treat ketoacidosis, etc. The potential benefits of treating metabolic acidosis with the administration of alkaline solutions (typically sodium bicarbonate) have not been supported in numerous investigations (53). However, when bicarbonate loss is the etiology of a non-anion gap acidosis, then administration of a bicarbonate equivalent (e.g., lactate, acetate, bicarbonate) is used to replace the losses.

Metabolic Alkalosis

The most common alkalosis abnormality in surgical critical illness is hypochloremic, hypokalemic metabolic alkalosis. The following factors promote this disturbance: (1) the common use of

Table 7.18 Etiologies of Metabolic Acidosis

Elevated Anion Gap	Normal Anion Gap
1. Lactic acidosis	1. Diarrhea
2. Ketoacidosis	2. Pancreatic fistula
3. Uremia	3. SB fistula
4. Toxins	4. Ureterosigmoidostomy
• Salicylate	5. Renal tubular acidosis
• Paraldehyde	6. Carbonic anhydrase inhibitor
• Ethylene glycol	7. Exogenous HCL
• Methyl alcohol	

Anion gap = Na – Cl – CO_2. Normal range = 8–12.

Table 7.19 Formulae for Strong Ion Difference Calculations

SID APPARENT: SIDa = $(Na^+ + K^+ + Ca_{2+} + Mg_{2+}) - (Cl^- + \text{lactate}^-)$

SID EFFECTIVE: SIDe = $2.46 \times 10^{-8} \times pCO_2$ (mm Hg)/10^{-pH} + [albumin (g/L)] × (0.123 × pH – 0.631) + [phosphate (mg/dl)] × (0.309 × pH – 0.469)

Strong Anion GAP (SIG) = SIDa – SIDe. This calculation accounts for the weak acids, mostly albumin, that can be altered in critical illness.

nasogastric suction in the post-operative period that removes chloride (chloride depletion); (2) the trauma of surgery and hypoperfusion that stimulates aldosterone and cortisol release (augmented mineralocorticoid state); (3) the in-hospital use of loop diuretics and the resultant hypokalemia; (4) diminished glomerular filtration (54). The most common type of hypochloremic metabolic alkalosis is the chloride responsive type (Table 7.20).

In difficult cases, the urine chloride concentration may help determine whether the metabolic alkalosis fits into the chloride responsive or resistant type. Alkalosis associated with hypochloremia is not based simply on the absolute chloride concentration, but rather on the chloride concentration relative to the concentration of sodium. For instance, an individual with a serum sodium of 145 will likely be alkalotic with a chloride of 105 even though the chloride is normal. Similarly, a patient with a chloride of 90 but a serum sodium of 120 will not be alkalotic even though the chloride is low. This is because the difference between the sodium and chloride is important, not the absolute level of the chloride itself.

Adverse effects of metabolic alkalosis are listed in Table 7.21.

Besides correcting the underlying etiology, the treatment of chloride responsive hypochloremic hypokalemic metabolic alkalosis is listed in Table 7.22. Most often, replacing chloride as NaCl (0.9% saline) and KCl (40 Meq/L) is adequate for the therapy (194 chloride Meq/L). Inhibition of bicarbonate reabsorption with acetazolamide is very effective when potassium chloride or other chloride salts cannot be sufficiently administered (55).

Table 7.20 Etiologies of Metabolic Alkalosis

Chloride Responsive	Chloride Resistant
Gastric suction	Hyperaldosteronism
Diuretics—mild K^+ depletion	Adrenal hyperplasia
Post-hypercapnic	
Reduced GFR	
Physiologic aldosterone secretion	Severe K^+ depletion

Urine Cl– concentration. Chloride response <10–20 Meq/L. Chloride resistant >10–20 Meq/L.

Table 7.21 Adverse Effects of Metabolic Alkalosis

I. CNS
   Delirium
   Lethargy
   Seizures
   Neuromuscular irritability
   Hepatic coma
II. Pulmonary
   Hypoventilation – carbon dioxide retention
III. Cardiac
   Q-T prolongation
   U waves
   Arrhythmias

Table 7.22 Treatment of Hypochloremic, Hypokalemic Metabolic Alkalosis

1. Cl^- and K^+ usually as NaCl and KCl
2. Carbonic anhydrase inhibition

Common Electrolyte Abnormalities

Hyponatremia

The most common pure electrolyte abnormality is hyponatremia. The etiologies of hyponatremia are listed in Table 7.23. The most common cause of hyponatremia in surgical critical illness is a combination of having increased vasopressin production from hypoperfusion/inflammation as well as losses of sodium both into the third space, and external losses such as nasogastric suction (56). This altered physiology combined with the administration of hypotonic fluids will characteristically decrease serum sodium concentrations.

Correction of hyponatremia is influenced by symptoms as well as the magnitude and duration of the alteration. The principal symptoms of hyponatremia are neurologic—headache, nausea, vomiting, delirium, neuromuscular depression, and seizures. Symptomatic hyponatremia (usually associated with serum sodium concentrations <125 Meq/L) is rare in surgical critical illness, but demands special caution during treatment to avoid brainstem injury (pontine and extrapontine demyelination). An increase in serum sodium no greater than 8 Meq/L in 24 hours is recommended, and the methods employed depend upon further characterizations that have been well reviewed elsewhere (56). Identifying and treating the underlying cause in the principal plan for durable therapy.

Table 7.24 lists etiologies of hyponatremia, which are laboratory values only and not true physiologic values. The most frequent cause of this is hyperglycemia.

Hypernatremia

Table 7.25 lists etiologies of hypernatremia. The surgical critical illnesses of head trauma and burn injury are most frequently associated with this alteration. Large volumes of 0.9% saline

Table 7.23 Etiologies of Hyponatremia

- Gain water in excess of sodium
  - Secretion of vasopressin
  - Administration of hypotonic fluids
- Loose sodium in excess of water
  - Adrenal insufficiency
  - Salt wasting nephropathy
- Combination of 1 and 2
  - Trauma and surgery with resultant fluid sequestration
  - Congenital heart failure
  - Cirrhosis with ascites
  - Diuretics

Table 7.24 Etiologies of "Spurious" Hyponatremia

1. Hyperglycemia
   - For each 100 mg% above a glucose of 100, expect a decrease of 1.6 Meq/L sodium
2. Hyperproteinemia

Table 7.25 Etiologies of Hypernatremia

1. Desiccation—most often in burns
2. Osmotic diuresis
3. High-output renal failure
4. Drainage of hypotonic fluids
5. Diabetes insipidus
6. Excessive sodium administration

with 154 sodium ions per liter can augment the incidence of hypernatremia (57). Adults rarely have symptoms until the serum sodium exceeds 160 Meq/L. Delirium, muscle weakness, and coma can develop.

When hypernatremia has developed over a few hours, then rapid correction (decrease in serum sodium of 1 Meq/L/hr) is safe. When the duration is many hours, days, or unknown, then a correction rate of 0.5 Meq/L/hr is safe, translating into a practical adjustment of 10 Meq/L in 24 hours (57). As with hyponatremia, identification and treatment of the underlying cause is a necessary adjunct to the correction of the electrolyte disturbance.

Hypokalemia

Mild hypokalemia (3.0–3.5 Meq/L) is usually asymptomatic. Concentrations of 2.5–3.0 Meq/L can be associated with muscle weakness and constipation. Levels less than 2.5 Meq/L can be linked to muscle necrosis and ascending paralysis. In patients with cardiac disease, mild to moderate hypokalemia is associated with arrhythmias, especially when digoxin is present (58).

As noted above, hypokalemia is a characteristic feature of hypocholemic alkalosis, and the administration of KCl is typically part of the management of that acid–base alteration. Other etiologies are listed in Table 7.26.

Of particular note is the association of hypokalemia (<3.6 Meq/L) with trauma, especially head injury, despite a metabolic acidosis rather than alkalosis (59). Acidosis and hypokalemia have been documented during post-operative hypothermia (60).

Hypokalemia following trauma appears to be secondary to elevated epinephrine blood levels and may be a marker of cellular insult (59) (61–63).

Hyperkalemia

Hyperkalemia can present an acutely life-threatening situation, the etiologies of which are listed in Table 7.27. The diagnosis of hyperkalemia often depends on a high index of suspicion and recognition of changes in the cardiogram as listed in Table 7.27. Table 7.28 outlines the treatment of hyperkalemia. The fastest onset of action is seen with the infusion of calcium (gluconate or chloride), which directly antagonizes the effect of potassium on the myocardium.

Table 7.26 Etiologies of Hypokalemia

I. Hypochloremic alkalosis
A. Loss of chloride
B. Diuretics
C. Mineralocorticoid excess
II. Magnesium depletion
III. Catecholamine excess

Table 7.27 Hyperkalemia

A. Etiologies of hyperkalemia
• Metabolic acidosis
• Renal failure
• Hemolysis
• Muscle injury (rhabdomyolysis)
• IV or PO intake
• Hypoadrenalism
B. EKG changes with hyperkalemia
• Peaked T waves
• Prolonged QRS
• Cardiac standstill

Table 7.28 Treatment of Hyperkalemia

Drug/Treatment	Dose	Onset
Calcium gluconate or calcium chloride	1–4 g IV	1–5 min
Sodium bicarbonate	44–88 mg	15 min
D^{50} W + insulin	50 ml + 10 units	15–30 min
Kayexalate	15 g PO or 50 g per enema	2+ hr
Peritoneal dialysis		2+ hr
Hemodialysis		15 min

Table 7.29 Calculation of Serum Osmolarity

$$\text{MOSM /L} = 2\,[\text{Na}^+]\,\text{Meq/L} + \frac{[\text{G1u mg/100}]}{20} + \frac{[\text{BUN mg/100}]}{3}$$

Normal = 285 to 295.

Table 7.30 Common Etiologies of Hyperosmolarity

1. Hyperglycemia
2. Elevated BUN
3. ETOH leading to inhibition of vasopressin
4. Desiccation (loss of H_2O in excess of Na^+)
5. Mannitol
6. Angiogram dye
7. Calcium

The underlying etiology must be treated directly, for example, alleviate the metabolic acidosis with the treatment of shock. Treating the acidosis per se is not likely to result in a durable effect. The management of rhabdomyolysis may require debridement of dead muscle. Sub acute therapy is directed at the removal of potassium via the GIT with Kayexalate. The hyperkalemia associated with renal failure is best treated with renal replacement therapy, and this may be needed acutely (64).

Hypomagnesemia

Magnesium (Mg) is principally an intracellular ion with 50–60% residing in the skeleton. Only 1% of total body magnesium is in the extracellular space, but serum Mg concentration (bound and unbound) is the common tool for assessing the Mg state of a patient. Epidemiologically, hypomagnesemia (both total and ionized) is frequent during surgical critical illness and has been associated with increased mortality (65,66).

Hypomagnesemia rarely occurs in isolation and is usually associated with hypokalemia and hypocalcemia, thus making symptoms and signs of hypomagnesemia difficult to tease out (67). However, cardiac repolarization abnormalities have been noted and ventricular arrhythmias have been attributed to low blood Mg concentrations. In addition, increased neuromuscular irritability with tremor, muscle twitching, and tetany have been reported (65).

While the etiologies of associated hypokalemia and hypocalcemia are commonly coexistent with those of hypomagnesemia, both hypokalemia and hypocalcemia can be resistant to therapy until Mg concentrations are normalized (65).

Osmolarity

In surgery, conditions may arise that increase or decrease the serum osmolarity so that the consequences of this must be dealt with from either a fluid and electrolyte aspect or from a renal aspect. Serum osmolarity may be calculated by the formula in Table 7.29. The etiologies of hyperosmolarity are listed in Table 7.30. The consequences of an osmotic load are listed in Table 7.31.

Table 7.31 Consequences of Osmotic Load

1. Elevation in serum osmolarity
2. Shift of intracellular fluid into interstitial space (hyponatremia—early)
3. CNS dysfunction
4. Diuresis with urine sodium 50 Meq/L (loss of more water than salt)
5. Volume contraction and hypernatremia—late

SELECTED METABOLIC DISTURBANCES

Surgical Critical Illness Hypoadrenalism

As discussed in detail in the section on "Inflammation," systemic inflammation is common in surgical critical illness and is usually secondary to such etiologies as infection, direct tissue damage, and ischemia/reperfusion. Inflammation resulting from any of these causes may have effects that are both positive (e.g., activation of host defenses and wound healing) and negative (e.g., suppression of host defenses, organ malfunction). Severe, persistent systemic inflammation is associated with the malfunction of many organs and an increased risk of death.

Many recent studies have investigated factors that promote (hypoperfusion, tumor necrosis factor production, interleukin (IL)-1 production) and decrease (improved perfusion, antagonists that inhibit cytokine release or function) severe systemic inflammation. As part of the stress response, blood levels of the endogenous glucocorticoid cortisol are characteristically increased and are usually >30 μg/dl. Cortisol exerts both metabolic and anti-inflammatory effects. Since absolute adrenal insufficiency decreases survival following acute insults, the effects of a physiological increase in cortisol concentration are presumably beneficial.

Severe adrenal insufficiency during surgical critical illness has been reported, usually associated with adrenal hemorrhage, infarction, or unrecognized adrenal suppression from prior steroid administration. However, over the past decades, several reports have suggested that lower than expected blood cortisol concentrations may be present during surgical critical illness without anatomical disruption or previous suppressive therapy (hypoadrenalism of surgical critical illness).

Pharmacologic doses of steroids (i.e., 30 mg/kg methylprednisolone every six hours) severely limit inflammation and may interfere with the desired effects. Physiologic doses of hydrocortisone (150–300 mg/day) in patients exhibiting a less than expected adrenal response to stress may limit the detrimental systemic effects of inflammation by replacing a deficit in an endogenous feedback system (68–71).

While this logic is intriguing and provides an inexpensive therapy for destructive inflammation, further study is needed to define the incidence, possible mechanisms, and potential benefits of this therapy, that is, the quest for the "eucorticoid" state as espoused by Beisel in 1969 (72). Interestingly, in high-risk cardiac surgery, the ratio of the cytokines IL-6 and IL-10 seem to provide a clue vis a vis achievement of the eucorticoid status (73).

Clues that hypoadrenalism may be present are listed in Table 7.32. Blood eosins are exquisitely sensitive to glucocorticoid effect such that stress usually induces counts close to zero (74). Therefore, eosinophilia (total eosin count >450) is especially uncommon in surgical critical illness, and unless an allergic cause or interstitial nephritis is apparent, can prompt investigation of adrenal status. Short of true eosinophilia, any increase in eosins during surgical critical illness raises the possibility of hypoadrenalism, although this is insufficiently specific to initiate therapy (75). Hyperkalemia is rare without accompanying renal failure and/or acidosis and when isolated from these alterations can indicate hypoadrenalism. Hyponatremia is fairly common and by itself would be least suggestive.

Clinical evidence of ongoing systemic inflammation after assessment and treatment of usual inflammatory diseases (i.e., pneumonia, intra-abdominal abscess) may be the most common prompt to investigate adrenal function. Patients who continue to exhibit such symptoms as fever, tachycardia, fluid sequestration, and respiratory failure after usual therapy is administered may have inadequate glucocorticoid function contributing to the ongoing inflammatory state.

Table 7.32 Clues to Adrenal Insufficiency

1. Eosinophilia
2. Hyperkalemia without renal failure or acidosis
3. Hyponatremia
4. Ongoing evidence of systemic inflammation (fever, tachycardia, fluid sequestration)

Table 7.33 Clinical Associations with Hypocalcemia (Ionized Calcium)

1. Hypovolemic hypoperfusion
2. Severe inflammation
3. Multiple blood transfusions
4. Renal failure
5. Albumin resuscitation

Table 7.34 Proposed Etiologies of Hypocalcemia During Surgical Critical Illness

1. Extracellular sequestration
   - Citrate infusion—massive transfusion
   - Parathyroidectomy—rare
   - Renal failure—elevated phosphate
   - Albumin resuscitation—not common
   - Metabolic alkalosis—not supported
2. Inadequate PTH Secretion—not Supported
3. Intracellular migration
   - Hypoperfusion
   - Severe inflammation

The assessment of adrenal function should include a baseline serum cortisol followed by an ACTH stimulation test (injection of alpha corticotropin 0.25 mg—a pharmacologic dose—with repeat cortisol 30 and 60 minutes later). Low baseline cortisol with increased cortisol (>9 µg/dl) following ACTH would indicate pituitary malfunction. No response to pharmacologic ACTH (<9 µg/dl) is usually considered diagnostic of adrenal depression, regardless of the basal concentrations. Interestingly, a poor response to ACTH in humans has been linked to higher concentrations of inflammatory mediators than a low basal cortisol concentration (76).

When a patient meets the selected diagnostic criteria for hypoadrenalism of surgical critical illness, therapy should be physiologic doses of hydrocortisone (150–300 mg/day). The specifics of administration and the duration have been controversial.

A continuous infusion provides several advantages: it emulates the endogenous adrenal response (loss of circadian rhythm, constant elevation); it allows for measurement of blood levels (half life of 40 minutes and a relative steady state after a few hours); glycemic control is more readily achieved (77,78).

By design, studies of hydrocortisone administration during severe systemic inflammation usually have arbitrary durations of several days (79). Whether these durations are optimum has not been investigated.

Hypocalcemia

Hypocalcemia (defined as decreased ionized calcium) is common in surgical critical illness and is associated with the conditions listed in Table 7.33. Importantly, the magnitude of decrease in ionized calcium is indicative of the severity of illness. Patients with the lowest ionized calcium levels at the time of intensive care unit admission are more likely to die, even though they die many days later. Hypocalcemia in this setting is associated with increased parathormone (PTH) levels and metabolic acidosis (80–82).

Proposed etiologies are listed in Table 7.34. Symptomatic hypocalcemia (i.e., perioral numbness, carpopedal spasm) is rare in surgical critical illness and implies a different

physiology for this hypocalcemia as compared to that seen after removal of the parathyroid glands. Increasing evidence demonstrates migration of extracellular calcium into the intracellular space, particularly following inflammatory insults such as pancreatitis or sepsis. In humans an increase in red cell and lymphocyte calcium has been documented during sepsis (83–86). The association of increased mortality risk with the lower ionized calcium levels is in keeping with the concept that a defect in cellular metabolism is responsible for this abnormality, which is reflective of the severity of cellular injury, that is, shock. The concentration of calcium outside the cell (10,000:1 gradient) demands active cell membrane function to maintain this gradient, similar to that needed for sodium homeostasis. Disturbances in cell energetics hinder active gradient functions and allow concentration-dependent movement of solutes.

While administration of calcium for hypocalcemia related to parathyroidectomy or poor citrate metabolism during massive transfusion is warranted, experimental data demonstrate increased mortality when calcium is provided during severe systemic inflammation (87,88). Excess intracellular calcium is toxic and considered a common mechanism of cell death from shock and, in particular, renal cell death following rhabomyolysis-induced intracellular calcium migration (32,89–91). Therefore, there is no documented benefit for calcium administration for ionized hypocalcemia that results from either hypoperfusion and/or systemic inflammation.

As a corollary to the concept that critical illness results in intracellular migration of calcium are reports of hypercalcemia occurring in surgical critical illness, particularly in the setting of AKI (92,93). This has been shown to develop in patients who previously had many episodes of hypocalcemia and usually at a time when the severity of critical illness is decreased. When this hypercalcemia develops, PTH levels are usually low, especially as compared to the elevated levels during the acute onset of the hypocalcemia. This suggests that previous intracellular migration of calcium results in a pool, which then migrates out of the cells when the illness is resolving and cellular metabolism improves.

Importantly, there is a subset of patients who demonstrate an elevated PTH during the hypercalcemia phase and are at particular risk for bradyarrhythmias. Treatment with bisphosphonate corrects the hypercalcemia and the arrhythmias risk (93,94). Therefore, patients who repeatedly exhibited a low ionized calcium early during surgical critical illness should have their ionized calcium periodically remeasured. If it is found to be elevated, then a PTH level will distinguish the at-risk group.

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8 | The gastrointestinal system

BASIC PHYSIOLOGY

The reader is referred to gastrointestinal disease textbooks to review the basic physiology of the intestinal tract. This chapter will highlight gastrointestinal pathophysiology linked principally to surgical critical illness.

THE RESPONSE TO HYPOPERFUSION

Diminished cardiac output sufficient to stimulate "flow receptors" results in the activation of neuroendocrine mechanisms that increase peripheral resistance (see chap. 3). The gastrointestinal tract (GIT) is the principal location of this increase in resistance. Activation of the sympathetic nervous system and constriction of GIT afferent arterioles result in a proportional reduction in intestinal blood flow (i.e., if cardiac output is decreased by 25%, this process decreases intestinal blood flow by 25%). However, activation of angiotensin II and vasopressin release results in a disproportionate reduction in perfusion via further arterial constriction. Hypersensitivity of mesenteric arteries to angiotensin II appears to be the principal mechanism of this response (1).

Once in place, hypoperfusion may result in the alterations listed in Table 8.1. Most of these alterations are anatomic (i.e., direct cell injury from hypoxia), but with lesser decreases of insult physiologic disturbances can develop (e.g., ileus, translocation) (2).

THE RESPONSE TO INFLAMMATION

Since inflammation begets hypoperfusion, severe systemic inflammation may result primarily in a global or regional decrease in perfusion to the splanchnic organs, thereby producing hypoxic injury. However, following hypoperfusion the GIT is a potent site of reperfusion physiology (hypoperfusion begets inflammation). Toxic oxygen moities as well as activation of inflammatory mediators and cells can result in apoptosis of intesintal lymphatic and mucosal cells along with disturbances in GIT function that may or may not be associated with anatomical damage (Table 8.2) (3–8).

Similar to the effect of severe hypoperfusion, severe inflammation can interfere with the mucosal barrier function of the GIT that prevents the migration of microorganisms and the breakdown products of microorganisms from gaining access to extraluminal sites (e.g., peritoneal cavity, lymph nodes draining the GIT, portal blood). Many insults that result in inflammation (e.g., ischemia/reperfusion, burns, endotoxin, infusion of live bacteria) increase the migration of intestinal organisms or inflammatory mediators across the lumen (9–11).

Despite evidence of decreased blood flow during inflammation, severe inflammation can affect the liver differently from severe hypoperfusion alone. Microscopic examination of liver tissue of patients suffering from severe inflammation can demonstrate intrahepatic cholestasis rather than the centrilobular necrosis that is characteristic of isolated hypoperfusion. Several experimental studies have documented altered hepatic metabolism and cholestasis following ischemia/reperfusion and severe inflammatory insults that develop despite well maintained or increased regional blood flow. Therefore, severe inflammation may result in hepatic insults that are not primarily hypoperfusion induced (12–15).

SPECIFIC GASTROINTESTINAL DISEASE STATES (TABLE 8.3)

Esophageal Hemorrhage

Esophageal varix hemorrhage occurs most often in patients with severe liver disease and results in further deterioration of the metabolic, hemodynamic, hematologic, and renal alterations already present. The management of esophageal variceal bleeding usually follows the sequence of steps listed in Table 8.4, although balloon tamponade may be necessary before endoscopic procedures can be applied. The non-operative intervention of a transinternal

Table 8.1 Gastrointestinal Alterations Secondary to Hypoperfusion: Too Little Oxygen Delivery

1. Stomach/duodenum
   - Gastritis/duodenitis
   - Ulcer
   - Bleeding
2. Gallbladder
   - Acalculous cholecystitis/necrosis
3. Liver
   - Centrilobular necrosis
4. Pancreas
   - Pancreatitis
5. Small bowel
   - Translocation
   - Ileus
   - Ischemic necrosis/partial or full thickness
6. Large intestine
   - Ileus
   - Ischemic necrosis/partial or full thickness

Table 8.2 Inflammation-Induced Gastrointestinal Tract Alterations

1. Gallbladder
   - Acalculous cholecystitis
2. Small bowel
   - Ileus
   - Translocation
   - Mucosal injury
3. Liver
   - Intrahepatic cholestasis
4. Pancreas
   - Pancreatitis
5. Colon
   - Mucosal injury

Table 8.3 Common Gastrointestinal Problems in the Surgical Intensive Care Unit

1. Esophageal
   - Varices
   - Mallory–Weiss tear
2. Stomach and duodenum
   - Stress gastritis
   - Ulcer
3. Liver and biliary tree
   - Jaundice
   - Liver failure
   - Acute acalculous cholecystitis
4. Pancreas
   - Pancreatitis
   - Infected pseudocyst
   - Infected pancreatic necrosis
5. Small bowel and colon
   - Diarrhea
   - Decreased barrier function—the GIT as a reservoir for repeated inflammatory insults
6. Intra-abdominal abscess (other than pancreatic)

Table 8.4 Medical Management of Variceal Hemorrhage

I. Drug-induced reduction in portal pressure
A. Octreotide
B. Vasopressin
C. Beta blockade
II. Local control of varix tissue
A. Banding
B. Sclerosis
C. Tamponade
III. Prophylactic antibiotics
IV. Anatomical reduction in portal pressure
A. Tips
B. Surgical shunt

jugular portal-systemic shunt (TIPS) has the advantage of decompressing the portal venous system without the potential deleterious effects of major abdominal surgery. Surgical shunt procedures are rarely performed. Early TIPS appears to be advantageous, especially in patients with advanced liver disease (16,17).

Mallory–Weiss tear hemorrhage is usually controlled with conservative measures, which may include vasopressin infusion.

Stomach and Duodenum

As stated above, following any etiology of hypoperfusion and severe inflammation, the entire intra-abdominal GIT supplied by the celiac axis and the superior and inferior mesenteric arteries suffers insults that may be disproportionally large, as compared to the heart, lungs, and brain. Since the GI mucosa is the most actively metabolic layer, the mucosa suffers the most from metabolic insults. The damaged mucosa becomes more susceptible to other insults such as acid, steroids, non-steroidal anti-inflammatory drugs, and, possibly, components of bile and/or pancreatic secretions (18).

In the stomach and duodenum, this mucosal damage can be clinically manifest as gastritis, duodenitis, gastric ulcers, and duodenal ulcers (19). These alterations can result in upper intestinal bleeding and are seen at the time of diagnostic upper endoscopy. However, stress damage is not necessarily limited to the mucosa. Full-thickness damage and perforation are also possible, but very rare.

The most convincing evidence that acid promotes the "stress" injury in the stomach and duodenum is that controlling gastric pH significantly reduces upper GI bleeding in critically ill surgical patients (20). Prior use of antacid has been replaced with the use of histamine-2 receptor antagonists (HRAs) or proton pump inhibitors (PPIs). At present, PPIs have not been shown to be more effective than HRAs and the application of any acid inhibition has been questioned for patients receiving enteral nutrition (21,22).

The concept of direct mucosal protection with sucralfate without acid inhibition gained popularity in the 1990s, especially when infectious disease frequency (e.g., pneumonia) seemed reduced (23). Subsequent investigations in trauma patients have failed to support this distinction (24,25). However, if all mechanically ventilated patients are included for study, regardless of the reason for ICU admission, then sucralfate may provide protection against pneumonia (26).

Liver and Biliary Tree

Jaundice

Jaundice is quite common during surgical critical illness and can be secondary to many factors (Table 8.5). The measurement of common liver tests usually provides an indication of jaundice that is associated with hepatocyte necrosis (marked aspartate aminotransferase and alanine transaminase elevations). Such hepatocellular damage is more consistent with severe

Table 8.5 Etiologies of Post-operative Jaundice

- Multiple blood transfusions
- Liver hypoperfusion
- Hematoma resorption
- Drugs
- Hepatitis
- Severe systemic inflammation
- Extrahepatic biliary obstruction

hypoperfusion ("shock" liver) and hepatitis. Acute, infectious hepatitis is not common in surgical critical care, but drugs, including alcohol, may cause direct hepatocellular insults.

Jaundice without significant aspartate aminotransferase/alanine transaminase elevation is quite common and may or may not be associated with increased alkaline phosphatase (AP) levels. An elevation primarily in unconjugated bilirubin without an elevation in AP would suggest hemolysis as a cause of jaundice. This can be further supported by measuring decreased haptoglobin levels and increased urine free hemoglobin. Jaundice with an elevated conjugated bilirubin and an equivalent increase in AP (i.e., bilirubin of 4 mg/dl associated with an AP of 400 units/L) suggests cholestasis of extrahepatic origin. When conjugated bilirubin increases rapidly without a comparable increase in AP or gamma glutamyltransferase, this is often a manifestation of intrahepatic cholestasis secondary to severe inflammation remote from the liver and biliary tree (i.e., pneumonia, necrotizing soft-tissue infection) (27).

Regardless of the pattern of bilirubin and/or AP elevation, evaluation of the biliary tree using a non-invasive approach like ultrasound is reasonable to assess the possibility of extrahepatic obstruction in any critically ill, jaundiced patient. However, except for the occurrence of acalculous acute cholecystitis, there is little reason to expect an extrahepatic biliary tree disease in most critically ill surgical patients who develop jaundice without a prior injury or surgical disease related to the liver or biliary tract.

Manifestations of Liver Failure (Table 8.6)

Liver test alterations may be the predominant manifestation of hypoperfusion/severe inflammation-induced organ malfunction. However, liver failure sufficient to result in life-threatening deficits is much more likely when severe hypoperfusion/inflammation impinge on a liver that is already diseased.

The magnitude of preexisting liver disease is frequently categorized using Child's criteria and/or the model for end-stage liver disease (MELD) score (Table 8.7) (28). Mortality risk in surgical patients is directly linked to the severity indicated by these classifications (28,29). Interestingly, for medical intensive care unit (ICU) patients, mortality risk is better linked to multiorgan failure analysis than liver failure, per se (30). In addition, severe liver disease is frequently associated with the hypoadrenalism of critical illness (see chap. 7). Providing physiologic hydrocortisone replacement may have a benefit in this population (31).

Coagulopathy unresponsive to vitamin K and coagulation factor administration, hypoglycemia, and persistent elevation of lactic acid all portend a poor prognosis.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is diagnosed on the basis of a serum creatinine >1.5 mg/dl that does not decrease to <1.0 mg/dl following the administration of albumin and the discontinuation of diuretics. Type 1 HRS is designated as an increase in creatinine >2.5 mg/dl in less than two weeks. Type 2 HRS is indicated by a "stable" elevation or a gradually increasing creatinine up to 2.5 mg/dl over more than two weeks (32,33). Type 1 is associated with acute illness and has a worse prognosis.

Renal hypoperfusion from systemic and intra-renal vasodilation is considered the primary mechanism that is treated with the vasopressin analogue terlipressin. Acute hypovolemic states such as gastrointestinal hemorrhage and/or progressive systemic inflammation can

Table 8.6 Manifestations of Severe Liver Disease/Failure

1. Coagulopathy
   - PT unresponsive to vitamin K
   - WProlonged PTT
2. Hypoglycemia
3. Elevated lactic acid
4. Hepatorenal syndrome

Table 8.7 Child's Criteria

Child Class	Bilirubin	Albumin	Ascites	Nutrition	Encephalopathy
A	<2.0	>3.5	None	Excellent	None
B	2–3	3–3.5	Little	Good	Little
C	>3.0	<3.0	Marked	Poor	Marked

Meld Score

MELD = 3.78 × $\log_e$ (bilirubin in mg/dl) + 11.2 × $\log_e$ (INR) + 9.57 × $\log_e$ (creatinine in mg/dl) × 6.43.

demand augmentation of intravascular volume. Usually, albumin solutions are selected for patients with liver failure (33).

The use of TIPS fir HRS is controversial, with some reports indicating that improved renal function can increase the success of liver transplantation (32).

Ascites

Alcohol-induced cirrhosis is characterized by and increase in both pre- and post-sinusoidal resistance to sinusoidal blood flow. An increase in pre-sinusoidal pressure will principally augment portal pressure with little effect on the hepatic lobule, per se. Such an increase in hydrostatic pressure will result in a transudate from the surface of the intestinal tract drained by the portal vein. Post-sinusoidal obstruction will also increase portal vein pressure, but, in addition, hepatic lymphatics become distended and lymph can spill from the liver into the peritoneal cavity, resulting in ascites that is more characteristic of an exudate. Therefore, examination of ascites can result in measurements that do not clearly distinguish a transudate from an exudate (34).

Abdominal procedures in patients with ascites, exclusive of liver transplanation and porto-caval shunts, pose additional risks related to fluid and protein losses, tension on the abdominal wall, healing of anastomoses, and recurrent intra-abdominal infection. Typically, critical surgical illness does not allow sufficient time for ascites management strategies like diuretic administration and/or repeated paracentesis to be effective.

Compared to paracentesis, TIPS has been shown to be more effective and associated with better short-term survival (35). Elective abdominal surgery in cirrhotics with ascites appears to be less complicated in patients who undergo a pre-operative TIPS (36,37). Elective liver resection appears to be less complicated with the use of closed ascites drainage (38). No well-studied management plan for the critical surgical abdomen in patients with ascites is available. A choice between closed drainage and TIPS seems to be supported by the elective abdominal surgery literature.

Acute Acalculous Cholecystitis

Another manifestation of the "stress" injury to the GIT is acute acalculous cholecystitis (AAC). Decreased mucosal blood flow, increased inflammatory mediator production, and decreased gallbladder contractile function have all been associated with AAC (2,5).

Most often seen in males who have been injured, AAC may become clinically evident several days after an insult, with a spectrum ranging from vague clinical manifestations, such as fever and jaundice, to frank right upper-quadrant peritonitis. Usually, the diagnosis requires a high index of suspicion in critically ill patients who are often sedated and/or paralyzed. This disease is primarily a condition that results from direct damage to the gallbladder wall rather than indirectly from pressure increasing in the gallbladder lumen. Therefore, the precise diagnosis typically requires direct inspection of the gallbladder wall rather than the use of less invasive techniques. As a consequence, ultrasound and cholecystographic scans are not as useful as in calculous acute cholecystitis. Both are subject to a high false-positive rate in surgical critical illness. A normal scintigraphy scan, however, makes the diagnosis extremely unlikely (2,5,39).

Since the diagnosis is best discerned based on the appearance of the gallbladder wall, a high index of suspicion may require direct inspection of the gallbladder. This can be accomplished with laparoscopy when a patient can tolerate general anesthesia and abdominal insufflations, or can be accomplished by a minilaparotomy under local anesthesia. With either technique, if the gallbladder looks normal, no intervention is needed. If the gallbladder wall looks viable but the gallbladder is markedly distended, a cholecystostomy tube can be placed. If the gallbladder is abnormal, the gallbladder should be removed (40).

Some authors advocate the percutaneous drainage of the distended gallbladder in the critical care setting, and claim it as a treatment for acalculous cholecystitis. Since the specific diagnosis of acalculous cholecystitis requires inspection of the gallbladder wall, it is difficult to interpret the sensitivity and specificity claims of such reports. If the gallbladder wall is severely diseased, simple decompression is inadequate therapy and cholecystectomy is required. Therefore, any patient subjected to percutaneous gallbladder drainage who does not improve as expected should have the gallbladder directly visualized to assess this diagnosis and the effects of the tube decompression (41).

Acute Pancreatitis

The common etiologies of acute pancreatitis along with potential etiologies encountered in the surgical ICU setting are listed in Table 8.8.

Hypoperfusion

Perhaps no other acute abdominal condition is as potent an example of the intimate linkage between hypoperfusion and inflammation as is acute pancreatitis (hypoperfusion begets inflammation, inflammation begets hypoperfusion). Pancreatitis can be caused by hypoperfusion and can result in hypoperfusion (42–44).

The principal mechanism of hypoperfusion from pancreatitis is plasma volume depletion from "third space" losses (see chap. 4 and 7) (42,45–47). As with any systemic inflammatory process, myocardial depression is possible, but much less likely (48).

The severity of pancreatitis is the major determinant of associated physiologic disturbances and has been classically categorized by Ranson's clinical criteria (Table 8.9). However, Ranson's and other methods of severity designation often fail to provide early identification of severe acute pancreatitis (SAP), that is, a diagnostic designation when the patient is first seen. Certainly, parameters such as those listed in Table 8.10 would alert the clinician about the severity of the pancreatitis (45). But, none of these alterations might be present early and only emerge over the next hours to a few days. Therefore, the most practical and effective tactic is to assume that each case that is not already severe will become severe (42,45).

In practical terms, this means frequent monitoring of vital signs (every 1–2 hours) and urine output (use a bladder catheter), administration of lactated Ringer's solution expecting to provide at least 3,600 cm^3 during the first 24 hours, and repeated monitoring of variables linked to severity: arterial oxygen saturation, hemoglobin concentration, blood urea nitrogen and creatinine, acid-base status, and ionized calcium (49,50). An accelerated rate of isotonic fluid administration may be necessary at first (500–1,000 cm^3/hr), especially if plasma volume and circulatory threats are evident (42). Monitoring hemoglobin concentration is particularly useful, with the admonition to avoid any increase that would indicate further plasma volume depletion (49).

Table 8.8 Etiologies of Acute Pancreatitis

1. Common
   - Alcohol
   - Gallstones
   - Trauma
2. ICU related
   - Cardiopulmonary bypass
   - Major abdominal aortic surgery

Table 8.9 Ranson's Criteria of Pancreatitis Severity

1. At the time of admission
   - Age >55
   - Glucose >200 mg/dl
   - WBC >16,000
   - LDH >700 IU
   - SGOT >250 SFU.
2. At 48 hours
   - Calcium <8 mg/dl
   - BUN increase>5 mg/dl
   - HCT fall >10
   - Base deficit >4 meq/L
   - Arterial PO2 <60 mm Hg (room air)
   - Fluid sequestration >6L

Table 8.10 Early Indicators of Severe Pancreatitis

- Hypotension
- Oxygen saturation <90% on room air
- Generalized peritonitis
- Elevated hemoglobin concentration
- Elevated BUN/creatinine
- Increased lactic acid
- Decreased ionized calcium

Abbreviation: BUN, blood urea nitrogen.

SAP requires ICU monitoring and therapy for any or all the problems listed in Table 8.10. Once again, early plasma volume augmentation, with the expectation that most of the isotonic fluid administration will happen in the first hours, is associated with better outcomes (51). As evidenced by these recent investigations, the application of "goal directed" resuscitation for the severe systemic inflammation of pancreatitis would appear as beneficial as the same concepts for infection-induced severe systemic inflammation. Therefore, monitoring lactic acid and central venous oxygen saturation can be practical adjuncts during ICU monitoring. However, once the goal(s) is(are) achieved, there is little benefit to continued augmentation of plasma volume, a circumstance similar to the fluid management strategy for ARDS (52,53).

SAP can result in an additional process of circulatory disturbance, the abdominal compartment syndrome (ACS—see chap. 5). Intra-abdominal hypertension (IAH) is associated with more severe disease as well as augmented fluid sequestration, organ failures, and decreased blood calcium concentrations (54,55). Therefore, monitoring of intra-abdominal pressure is as practical as following vital signs, urine output, and laboratory parameters and should be initiated early (56). Abdominal decompression appears to be the most beneficial during the "resuscitation" phase of SAP (i.e., first few days) rather than later in the course (55).

Inflammation

While hypoperfusion and oxygen debt accumulation are well linked to morbidity and mortality, pancreatitis-induced severe systemic inflammation is an equally potent mechanism for organ failure and death (57,58). Respiratory deficiencies can be associated with pancreatitis-induced pleural effusions and atelectasis, but ARDS is the more life-threatening pulmonary disorder during SAP and is associated with the circulation of pancreatic enzymes as well as pro-inflammatory cytokines, neutrophil migration, etc (59). The clinician needs to be alert to the probability of ARDS during SAP and not treat the pulmonary malfunction as hydrostatic edema from heart failure (see chap. 6). Depletion of plasma volume using diuretics contradicts the fundamentals of hemodynamic support for SAP described above.

Acute kidney injury during acute pancreatitis is as likely caused by severe systemic inflammation as a consequence of hypoperfusion secondary to decreased cardiac output and/or the abdominal compartment syndrome (60). Other features of multisystem organ failure (hepatic, coagulation, and neurologic disturbances) are common, especially during SAP, and principally linked to systemic inflammation (57).

Despite the recognition that SAP induces severe systemic inflammation, treating the pancreatic inflammation directly has had little, if any, clinical application.

Potential for Augmented Systemic Inflammation

Two additional processes may augment systemic inflammation during SAP—rhabdomyolysis and hypoadrenalism (61–63). The etiology of muscle injury is obscure and not confined to any anatomical region. Rhabdomyolysis can aggravate systemic inflammation, renal damage, and intracellular calcium accumulation. Hypoadrenalism (see chap. 7) has been reported in about 30% of patients with SAP and associated with pancreatic necrosis and increased mortality. Whether or not exogenous hydrocortisone can ameliorate the severity and organ failure risks of SAP has not been determined.

Infectious Complications of Acute Pancreatitis

SAP can result in necrosis of pancreatic as well as peri-pancreatic tissues. The propensity for this necrosis to become infected with nearby intestinal organisms is associated with more organ failure (64). Patients who come to the diagnosis of infected pancreatic necrosis after about three weeks appear to have a better prognosis, but prophylactic antibiotics do not promote this delay to diagnosis (45,65–67). Image-guided fine needle aspiration of a site or sites worrisome for infection is the primary method for the diagnosis of infected pancreatic necrosis. Recently, the use of C-reactive protein and white blood count (WBC) has been offered as a tool to distinguish infected from non-infected necrosis, beginning at about three weeks after onset. A C-reactive protein <81 mg/L with a WBC <13,000/mm^3 were associated with a 1.4% risk of infected necrosis (56).

Once the diagnosis of infected pancreatic necrosis is established, operative debridement and drainage is the procedure of choice. The techniques employed depend upon the location of the necrotic material and the potential for adjunct interventions (e.g., feeding tube placement, loop ileostomy). When the process is located principally in the left retroperitoneal region, then percutaneous drainage of any liquified material followed by a minimally invasive necrosectomy may be feasible (68).

Most often, when a diagnosis of infection cannot be established, continuing non-operative management is recommended (64,69).

Nutrition

Enteral, preferably jejunal, feeding is recommended once the resuscitation phase is accomplished. Total parenteral nutrition (TPN) can be delayed several days with the hope that effective enteral access will be established (45,65).

Gallstone Pancreatitis

Biliary tree interventions for gallstone pancreatitis have included early endoscopic retrograde cholangio-pancreatography (ERCP), cholecystostomy, cholecystectomy, common bile duct exploration, and operative sphincterotomy. Over the past several decades debate has centered on the necessity and timing of ERCP and cholecystectomy, with operative approaches to the common bile duct becoming very rare. Early ERCP (shortly after diagnosis) is beneficial for patients with persistent bile duct obstruction and the additional diagnosis of cholangitis that demands bile duct decompression. Otherwise, there is no advantage (70,71). For patients with SAP, cholecystectomy can await resolution of the acute process or accompany later interventions, like drainage of a pancreatic pseudocyst after six weeks of observation (72).

Small Bowel and Colon

Many potential small bowel and colon problems (e.g., obstruction, fistula, anastomotic leak) may be encountered in the surgical ICU. Most of these relate to the underlying surgical disease or surgical intervention. Both accurate diagnosis and expeditious management of these conditions are important to surgical critical care, but are better discussed in the context of the specific diseases and surgical procedures. However, there are intestinal processes that are particularly germane to surgical critical illness.

Gut Permeability and Translocation

As stated in the section on "Basic Physiology," hypoperfusion and systemic inflammation can disturb the barrier function of the GIT, thereby allowing the migration of organisms, breakdown products of organisms, or other toxic materials to gain access to intestinal lymph, portal blood, and the peritoneal cavity. Proper GI barrier function necessitates normal intestinal flora (ecologic barrier), intact mucous epithelia (mechanical barrier), and effective immune cells with their secretions (immune barrier) (11,73).

Surgical critical illness commonly results in the administration of antibiotics that will alter GI microflora as well as stomach acid suppressants that promotes the emergence of these alterations in the proximal GIT (74). Hypoperfusion and ischemia/reperfusion damage the mucosa epithelial barrier as well as the gut-associated lymphatic tissue (GALT), thereby suppressing both the mechanical and immune barrier functions (11,73). Systemic inflammation from tissue injury can result in increased intestinal permeability (9,73,75). All these mechanisms impact principally the small bowel, a site not regularly exposed to such microbiologic challenge.

While passage of noxious luminal materials into mesenteric lymph is considered the principal pathway for translocation, documentation of intestinal organsims in portal blood and the peritoneal cavity in humans without necrotic bowel or perforations supports the concept that translocation can occur by other routes (see section on "Tertiary Peritonitis") (10,76).

Strategies to limit translocation include limiting antibiotics, especially therapy against anaerobes (73,77), effective resuscitation of the circulation to the intestinal tract, and enteral feeding (particularly with augmented glutamine administration) (78).

Diarrhea

The potential etiologies of diarrhea on the surgical ICU are listed in Table 8.11. Differentiating a secretory versus an osmotic diarrhea is usually simple. If diarrhea continues after stopping intestinal feeding, the diarrhea is secretory.

Clostridium difficile colitis is the most worrisome secretory diarrhea in surgical critical illness. The incidence and severity of this infection appears to be increasing and may be linked to a more virulent strain. Surgeons encounter *C. difficile* associated disease (CDAD) after performing intestinal procedures and also in hospitalized medical patients (79). The diagnosis of CDAD is usually secured by documenting the related toxin in a stool sample. However, some patients do not exhibit diarrhea, and a diagnosis of severe colitis becomes evident by abdominal imaging.

Fulminant CDAD is a surgical illness and markers of the risk of fulminant disease are listed in Table 8.12. The mortality risk of fulminant CDAD has been associated with the parameters in Table 8.13 (79). Simply stated, if a patient comes to the ICU because of CDAD, then the disease is fulminant. If a patient is already critically ill and develops CDAD, then the designation of fulminant disease may be more challenging.

Non-fulminant CDAD can be managed by the administration of metranidazole (by mouth or intravenous) and vancomycin by mouth. For ICU patients, usually both are provided.

The "traditional" surgical management of fulminant CDAD is a total abdominal colectomy and ileostomy, sometimes with a distal mucus fistula for topical vancomycin administration (79). Recently, the necessity of surgical extirpation has been challenged and the use of a loop ileostomy for colonic irrigation and then topical vancomycin administration has been associated with promising results (80).

Table 8.11 Intensive Care Unit Diarrhea

1. Secretory
   - Intraluminal inflammation
     - *Clostridium difficile* colitis
     - Antibiotic-associated diarrhea
     - Inflammatory bowel disease
   - Extraluminal disease
     - Partial small bowel obstruction
     - Intra-abdominal abscess
   - Short gut—inability to absorb endogenous secretions
2. Osmotic
   - Bowel edema—low serum albumin
   - Ischemia
   - Severe inflammation
   - Diminished small bowel surface
   - Diminished large bowel surface
   - Decreased fat absorption

Table 8.12 Markers of Risk for Fulminant *Clostridium difficile* colitis

Age >65
Elevated lactic acid
WBC >16,000/μl
Surgery within 30 days
History of inflammatory bowel disease
Treatment with IVIG

Abbreviation: IVIG, intravenous immunoglobulin G.

Table 8.13 Predictors of Mortality During Fulminant *Clostridium difficile* Colitis

Hypoalbuminemia
Elevated lactate
Mental status changes
Acute respiratory failure
Acute renal failure
WBC >35,000/μl
WBC <4,000/μl
Vasopressor use

Extraluminal disease, especially partial small bowel obstruction, may produce a secretory diarrhea. Attention to abdominal physical findings and abdominal x-rays should establish this diagnosis, and the disease is usually treated by nasogastric decompression. Diarrhea may be the clue that an intra-abdominal abscess is developing. Diarrhea in this setting may result either via direct irritation of adjacent small or large bowel, or by producing a partial obstruction. Drainage of the abscess is the primary treatment.

Osmotic diarrhea is evident primarily when intestinal feeding is used. Since the bowel is supplied by the systemic circulation, bowel edema can develop because of hypoalbuminemia. Therefore, if systemic capillary leaking is not considered likely, the provision of albumin may help reduce osmotic diarrhea. Any process that interferes with mucosal function, such as ischemia, will enhance an osmotic diarrhea. Diminished small and large bowel surface may be adequate to absorb endogenous secretions but not tolerate the addition of feedings. Decreased fat absorption from diversion of bile and pancreatic secretions or ileal resection and the consequent reduction in bile salt secretion may result in malabsorption, which can be treated by eliminating long-chain triglycerides from the diet and using medium-chain triglycerides and carbohydrate as the main caloric sources.

Management of an osmotic diarrhea usually requires adjustment of the types, concentrations, and rates of foodstuff administered. For instance, an elemental diet may be better tolerated by a patient with deficient pancreato-biliary secretions. In addition, medications that inhibit intestinal motility may decrease an osmotic diarrhea by allowing more time for absorption of liquids and solids.

Intra-Abdominal Abscess

Critically ill surgical patients commonly have disease (secondary peritonitis) and/or procedures that result in contamination of the abdominal cavity with usual intestinal tract organisms. The risk factors for developing an intra-abdominal abscess are listed in Table 8.14. This list reads like a description of all risk factors related to infection, except that the surgical fundamentals of adequate debridement and hemostasis must be used even in the healthiest patients if the risk of infection is to be diminished following intra-abdominal surgeries.

Once the patient is recognized to be at risk, vigilance for early detection of new or recurrent intra-abdominal infection is necessary to allow prompt intervention. Clinical clues that suggest such infection are listed in Table 8.15 and are non-specific as to origin (i.e., pneumonia could result in the same findings). History and physical examination are the first tools to be used when evaluating the possibility of new infection from any location, and may suggest an abdominal focus (e.g., new onset of abdominal pain, abdominal distention, absent or decreased bowel sounds, localized tenderness). Few routine tests are discriminative for an intra-abdominal abscess (Table 8.16). Except for surgical exploration, the study that yields the best false-positive/false-negative rate is the abdominal computed tomography (CT) scan. CT also provides sufficient anatomic definition to discern if percutaneous, rather than operative drainage, is possible (81).

Table 8.14 Risk for Intra-Abdominal Abscess

- Degree of contamination
- Hypovolemic hypoperfusion
- Severe inflammation
- Age >55
- Cancer
- Steroids
- Inadequate debridement
- Intra-abdominal hematoma
- Diabetes
- Malnutrition

Table 8.15 Clinical Clues to New or Recurrent Intra-Abdominal Infection

1. Persistent fever and/or hypothermia
2. Persistent fluid sequestration
3. Elevated WBC with shift to the left
4. New organ malfunction
5. Glucose intolerance

Table 8.16 "Routine" Tests Consistent with Intra-Abdominal Abscess

1. Multiorganism bacteremia
2. Plain X-ray evidence consistent with an abscess
   - Pleural effusion
   - Gas bubbles that do not move with changing position
   - Mass displacing abdominal contents
   - Partial bowel obstruction

Drainage is the primary therapy for intra-abdominal abscess. The method of drainage should be individualized to a patient's disease. If a well-localized abscess is diagnosed by CT and can be approached percutaneously, this is preferred, as it allows treatment without general anesthesia and manipulation of intra-abdominal viscera. Surgical intervention is indicated in the following instances: when the diagnosis is highly suspected but cannot be localized, when multiple collections make percutaneous drainage impractical, or when significant visceral injury is likely via a percutaneous route.

Antibiotic therapy alone is inadequate therapy for an intra-abdominal abscess. Antibiotics treat the surrounding cellulitis and may decrease the systemic sequelae of an abscess. There is no arbitrary duration of antibiotic therapy for an intra-abdominal abscess. Antibiotic therapy should be continued until there is evidence that the surrounding cellulitis and systemic sequelae have abated, which usually occurs when the patient is afebrile and the leukocyte count is normal or approaching normal. Prolonged antibiotic therapy after resolution of cellulitis will not provide any therapeutic advantage and may augment the growth of resistant organisms both at the abscess site and elsewhere.

Tertiary Peritonitis

As described above, most intestinal illness and procedures will contaminate the abdominal cavity with commensal organisms that are normal intestinal flora (e.g., *Escherichia coli* and *Bacteroides fragilis*). Peritonitis that results from such contamination is termed secondary peritonitis and is typically polymicrobial. The polymicrobial aspect of secondary peritonitis helps distinguish this infection from primary peritonitis that develops in patients with ascites and is typically monomicrobial (81).

Tertiary peritonitis is contamination of the peritoneal cavity that persists or emerges at least 48 hours after the treatment of primary or secondary peritonitis, and/or the treatment of another infectious disease with antibiotics that kill normal intestinal flora. Potential mechanisms for tertiary peritonitis are listed in Table 8.17. Most important is the recognition of the patient at risk and the realization that the contaminating microflora is distinctly different from secondary peritonitis and that, in particular, intestinal anaerobic organisms are not prevalent (Table 8.18) (81). Typically, these organisms are multiresistant and not responsive to antibiotics used for primary and secondary peritonitis.

The diagnosis of tertiary peritonitis usually follows image-directed sampling of a peritoneal collection, be it abscess-like or ascites. When ultrasound and CT do not provide a sufficient prompt for sampling, the presence or absence of active peritoneal inflammation can be further investigated using diagnostic peritoneal lavage. A lavage fluid WBC >200/mm^3 is consistent with peritonitis (82,83).

Table 8.17 Mechanisms for Tertiary Peritonitis

Early contamination with resistant organisms
Hospitalized patients
Use of broad spectrum antibiotics before intestinal insult
New transmural contamination after initial procedure
Leak of anastomosis
Acute cholecystitis
Perforated ulcer
Translocation

Table 8.18 Microflora of Tertiary Peritonitis

Coagulase-negative staphylococcus
Hospital Gram-negative rods
Pseudomonas
Enterobacter
Serratia
Candida species
Enterococcus

Table 8.19 Hyperglycemia in Surgical Critical Illness

Activation of hypothalamic/pituitary/adrenal axis
Catecholamine release
Activation of inflammatory cytokines
Insulin resistance

The treatment of tertiary peritonitis is the same as for secondary—source control and appropriate antibiotics. This may necessitate drainage, debridement, diversion of intestinal contents, and extirpation of tissue. Careful identification of the new microflora and the associated sensitivity and resistance to antimicrobials is needed to direct antibiotic administration (81).

SURGICAL NUTRITION

As reviewed in the chapter 4, surgical critical illness in the Flow phase of shock is characterized by a metabolic response that results in increased resting energy expenditure (REE), oxygen consumption, and mixed fuel oxidation (40% from glucose, 40% from amino acids, 30% from fat) (84). REE for severe trauma and burns is about 1.5 times greater than for basal circumstances and for sepsis REE approaches a twofold increase (85–87). Hyperglycemia is also characteristic, even in non-diabetics, and is linked to the parameters listed in Table 8.19 (88). Skeletal muscle amino acids are a principal endogenous source of gluconeogenic substrate. Utilization of this resource is largely responsible for the profound negative nitrogen balance and loss of body cell mass (BCM) that accompanies a metabolism directed to acute phase reactant synthesis and the preservation of non-intestinal visceral protein (e.g., liver, heart) (84,87,89–91).

BCM is the metabolically active component of the body, containing the oxygen consuming, potassium-rich, glucose oxidizing, and work-performing cells. The magnitude of BCM loss is directly associated with mortality risk (87,91).

Nutritional tactics to limit BCM loss began with the administration of intravenous glucose, and subsequently, intravenous protein and evolved into TPN along with more aggressive methods of providing enteral nutrition (89,90,92,93). Over the past two to three decades, investigations have addressed the issues listed in Table 8.20.

Table 8.20 Surgical Nutrition Investigations

Enteral versus parenteral
Tight glucose control
Components of nutritional therapy
Timing of nutritional support
Modulation of the metabolic response

Abdominal trauma patients benefit from early enteral nutrition as compared with TPN, demonstrating decreased infectious complications, presumably because of improved local and systemic host defenses linked to better gastrointestinal barrier and GALT function. These effects appear to be generalizable to all acutely ill patients without an effect on mortality (92,94,95). Interestingly, early enteral nutrition (within 24 hours of admission) appears to improve intestinal carbohydrate absorptive function as compared to feeding after ICU day 4 (96).

Elevated blood glucose, especially in non-diabetes, is epidemiologically associated with poor outcomes in surgical patients. In selected surgical patient populations (principally cardiac surgery), perioperative morbidity and, possibly, mortality is reduced when blood glucose is lowered to at least <200 mg/dl with insulin infusions. The current recommendation is to target blood glucose control to the 100–140 mg/dl range (88).

Improved gastrointestinal barrier and GALT function from enteral nutrition as compared to TPN appears to be further augmented by diets enriched in glutamine, arginine, omega-3 fatty acids, and nucleotides. A further reduction in infectious complications and organ failure incidence and duration can be realized when these immune-enhancing additives are provided as part of a complete nutrition plan (the fundamental composition of an enteral diet) or as a small volume adjunct to a regular enteral diet (97–99).

For surgical critical illness, early enteral (<24 hours after admission) feeding is a benefit. The use of TPN for nutritional support is not expected to provide similar regional and/or global host-defense advantages as compared to intestinal feeding. Therefore, the more global aspects of nutrition support (e.g., meeting caloric and protein requirements) are provided by TPN.

Most surgical patients do not exhibit a threat of malnutrition in this global sense until several days after injury and/or illness. During the first few days (up to day 8), the provision of parenteral nutrition to meet some or full calorie and protein needs appears to be detrimental (100–102). Therefore, more diligence in achieving intestinal access and using enteral feeding should be the focus of early nutritional attention. If such access cannot be provided, then the use of parenteral nutrition can usually be delayed, except, possibly in the setting of malnutrition in place prior to the surgical critical illness.

Despite attention to nutritional support, the metabolic alterations in the Flow phase of surgical critical illness do not allow neutral or positive nitrogen balance and perfect preservation of BCM (103). This is strikingly evident in burn patients and most of the concepts and mechanisms utilized to modulate the metabolic response of the Flow phase have been studied in that population. Tactics such as the use of anabolic agents (recombinant human growth hormone, insulin-like growth factor 1, insulin growth factor binding protein 3, oxandrolone) to promote positive nitrogen balance, and β-receptor antagonist administration (propanalol) to diminish metabolic demand have produced encouraging effects (87). Unfortunately, the use of growth hormone in generic adult critical care patients resulted in increased mortality, an effect that might be linked to poor glucose regulation and the dosing of the hormone (104).

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9 | The nervous system

INTRODUCTION

The central nervous system (CNS) alterations that are common in surgical critical illness are listed in Table 9.1. The most common one is traumatic brain injury (TBI). A description of basic brain anatomy and cerebral oxygenation physiology serves as a practical underpinning to the understanding and management of several of these alterations.

Anatomy

Knowledge of the anatomy of the cerebral cortex, with sensory and motor loci, is important for assessing focal sensory and motor deficits. However, many etiologies of depressed mental status in surgical critical illness (e.g., diffuse axonal injury, brain hypoperfusion, narcosis) produce global alterations in cortical function that may or may not be associated with localized findings. Important for assessing altered mental status is an understanding of the anatomy of the reticular activating system (RAS), a diffuse group of neurons that extend along the central brainstem from the medulla to the thalamus (Fig. 9.1). RAS is stimulated by every major somatic and special sensory pathway and serves to activate the cerebral cortex. Since the RAS arises in the brainstem, knowledge of the anatomy of the brainstem is useful for evaluating the status of the RAS.

The brain is enclosed in a hard, rough chamber, which, while being protective, can be responsible for direct or "counter coup" injury (Fig. 9.2). The medial temporal lobe is positioned close to the midbrain, the path of the third cranial nerve and cerebral blood vessels (Fig. 9.3). Particularly, medial displacement of the temporal lobe is likely to interrupt first the function of the third cranial nerve, then the midbrain, and, subsequently, larger areas of the brainstem (Fig. 9.4).

The brainstem is divided into midbrain, pons, and medulla (Figs. 9.5 and 9.6). Brainstem nerves that are valuable to evaluate include the following: (1) the third for innervation of the medial rectus and parasympathetic innervation to the pupil; (2) the fifth for sensation to the cornea; (3) the seventh for motor to the eyelids; (4) the sixth for innervation of the lateral rectus; (5) the eighth for innervation of the vestibular apparatus; (6) the medial longitudinal fasciculus connecting the eighth to sixth and third; (7) the course of the sympathetic nervous system through the entire brainstem.

Consciousness requires cortical function and is not lost unless cortical function is diffusely diminished. Diffusely diminished cortical function may result either from direct, global disruption of cortical function or from disruption of the RAS in the brainstem. Since the cortex is more sensitive to metabolic disturbances than the brainstem (i.e., hypoglycemia, hypoxia), "cortical coma" is more likely to be "metabolic," whereas "brainstem coma" most often is secondary to pressure on or structural damage to the brainstem (1).

Physiology of Cerebral Blood Flow, Oxygen Metabolism, and Intracranial Pressure

The brain requires a continuous supply of oxygen and glucose to support the aerobic glycolysis necessary to maintain the integrity of brain neurons. The brain is proportionally more sensitive to decreased delivery of oxygen than decreased delivery of glucose. The cerebral metabolic rate of oxygen ($CMRO_2$) is a useful measure of brain metabolism and is calculated as follows:

$$CMRO_2 = CBF \times C(a–v)O_2$$

Where, CBF = cerebral blood flow; C = oxygen content; a, v = arterial, venous, respectively.

In adults who are awake, CBF approximates 50 ml/100 g tissue at $PaCO_2$ of 40 mm Hg. $CMRO_2$ is about 3.2 ml/100 g under these conditions. $CMRO_2$ may increase with activities such as seizures and decrease with drug-induced coma. Usually, CBF adjusts to meet alterations in

Table 9.1 Central Nervous System Alterations in Surgical Critical Illness

I. Head trauma
   A. Pathophysiology of brain injury
   B. Examination before and after the CT scan
   C. Management of intracranial and cerebral perfusion pressure
   D. Adjuncts for management
   E. Associated organ malfunction
II. Blunt cerebrovascular injury
III. Manifestations of spinal cord injury
IV. Neuromuscular disorder of surgical critical illness
V. Management priorities for patients with traumatic brain injury

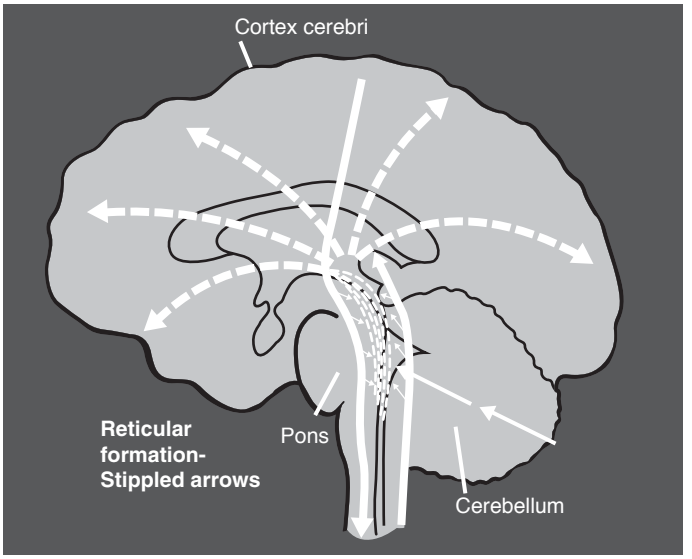

Figure 9.1 A schematic representation of the reticular activating system arising from the brainstem and projecting impulses cephalad throughout the cortex. *Source*: ACS. ATLS Student Manual. Chicago: ACS, 1997.

$CMRO_2$. However, severe brain injury may lead to disruption of the autoregulation of CBF such that too much or too little CBF may be supplied for the metabolic demands of the brain.

CBF is primarily determined by cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), as well as the arteriolar vascular resistance in the brain tissue. Therefore, CBF will increase if CPP increases and/or arteriolar resistance decreases, and it will decrease if CPP decreases and/or arteriolar resistance increases.

When CBF falls sufficiently such that more oxygen cannot be extracted (<23 ml/100 g), then $CMRO_2$ will decrease. First, the synaptic function ceases and then cell death ensues unless the normal metabolic demand of brain cells is reduced.

The equation for $CMRO_2$ shown above can be rearranged to the following:

$$C(a–v)O_2 = CMRO_2/CBF$$

This demonstrates that alterations in the arteriovenous content are secondary to alterations in $CMRO_2$ or CBF or both. Alterations in a–v saturation rather than the content have been argued to more accurately reflect brain oxygen status, especially when venous oxygen saturation is

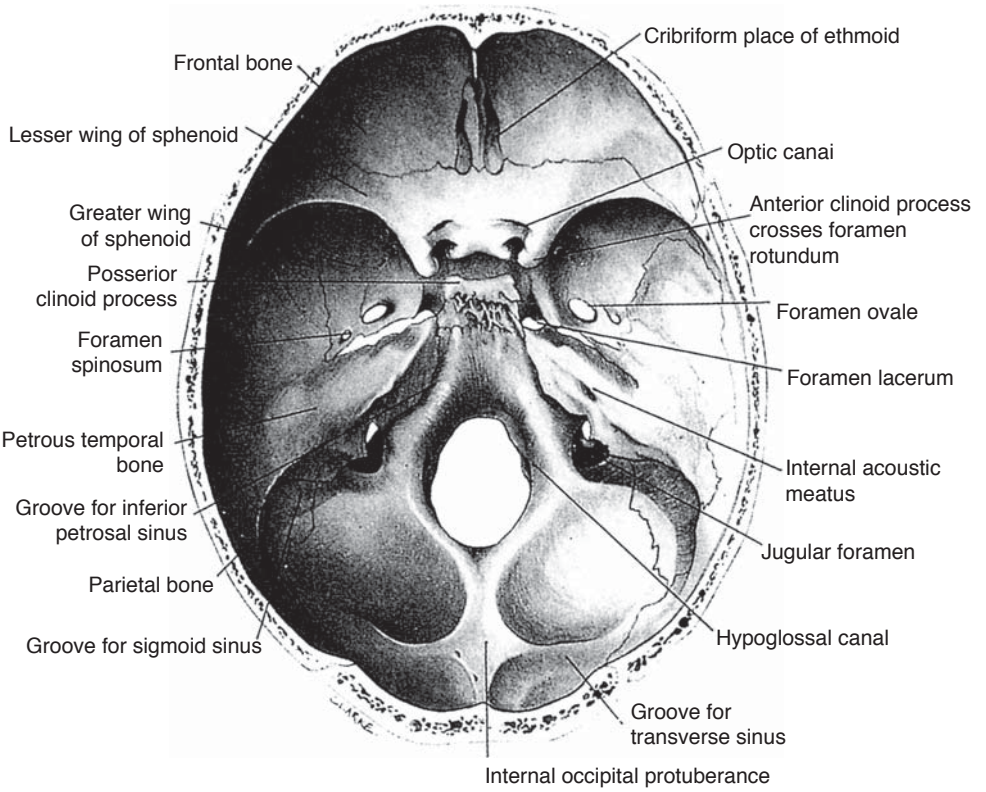

Figure 9.2 The interior of the base of the skull illustrating the bony prominences, which can result in direct or counter-coup injury to the brain. *Source*: Romanes CJ. Cunningham's Manual of Practical Anatomy. New York, NY: Oxford University Press, 1978.

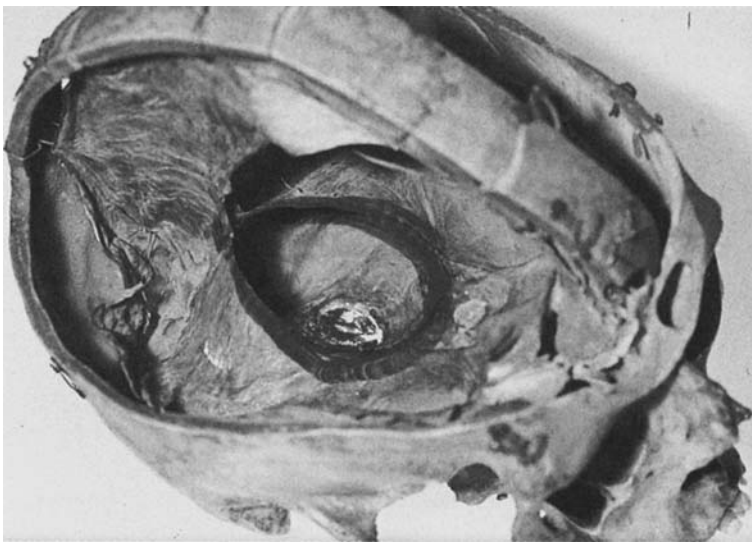

Figure 9.3 An open skull depicting the tentorium and the position of midbrain in juxtaposition to the medial, anterior tentorium, and adjacent to the location of the temporal lobe. *Source*: ACS. ATLS Student Manual. Chicago: ACS, 1997.

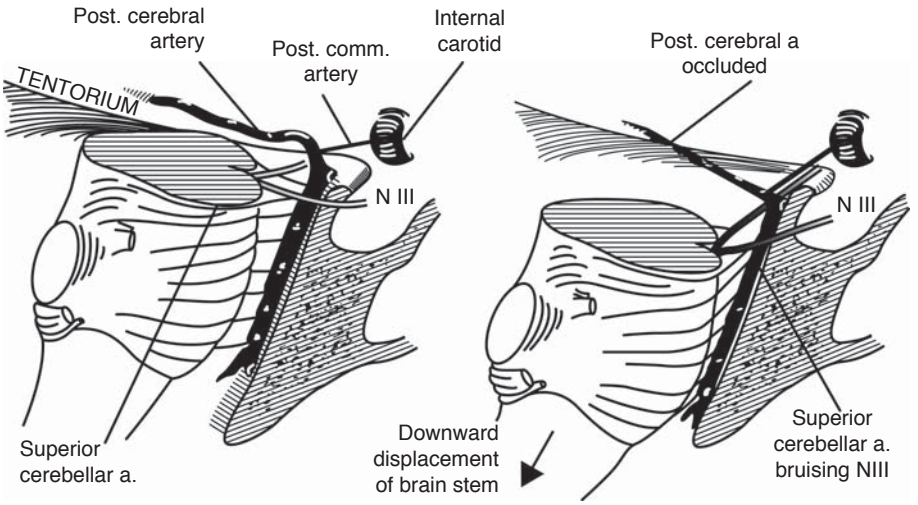

Figure 9.4 A schematic representation further depicting the close application of the tentorium and, therefore, the temporal lobe to the midbrain, the oculomotor nerve and the brainstem circulation. *Source*: ACS. ATLS Student Manual. Chicago: ACS, 1997.

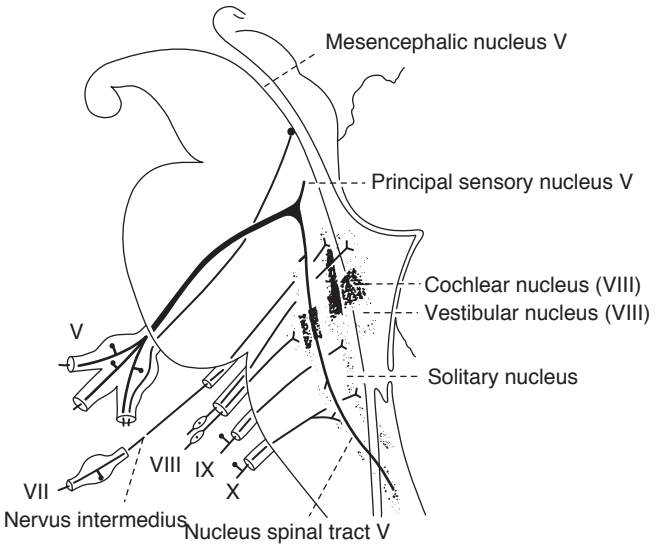

Figure 9.5 A schematic representation of the sensory nerves of the brainstem with the midbrain devoid of major sensory nerves, the pons with the fifth nerve, important for the corneal reflex, and the eighth nerve at the pontomedullary junction, important for the oculocaloric reflexes. *Source*: Gray's Anatomy, 28th edn. Baltimore: Lea & Febinger, 1968.

low, indicating increased oxygen extraction. Continuous measurement of jugular oxygen saturation ($SjvO_2$) has been used as a monitor of global cereberal oxygen delivery and consumption, especially in patients with TBI. Normal jugular venous oxygen saturation is 55–71%. Values <50% are usually secondary to decreased delivery rather than increased consumption (2–4).

Direct measurement of brain tissue pO_2 ($PbtO_2$) is also under investigation as a cerebral metabolism monitor. Normal brain pO_2 is in the range of 37 mm Hg, with severe hypoxia identified by values of 8 mm Hg or less. $PbtO_2$ may be influenced by regional as well as global reductions in CBF (4).

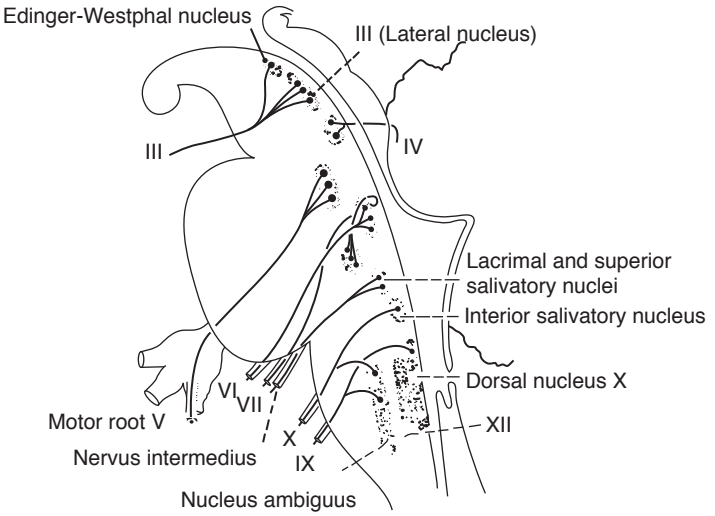

Figure 9.6 A schematic representation of the motor nerves of the brainstem, with the midbrain contributing the Edinger–Westphal nucleus for parasympathetic innervation of the pupil, and the third nerve that is important for oculovestibular and oculocaloric reflexes. The pons contributes the sixth nerve, also important for oculovestibular and oculocaloric reflexes, as well as the seventh nerve that is important for the corneal reflex. *Source*: Gray's Anatomy, 28th edn. Baltimore: Lea & Febinger, 1968.

Table 9.2 Determinants of Increased Intracranial Pressure

1. Increased CSF
   - Obstructed flow—occlusion of third ventricle
   - Obstructed reabsorption—occluded arachnoid granulations
2. Increased brain cell volume
   - Trauma—contusion
   - Hyponatremia
   - Hypoxia—hypoperfusion
   - Infection—Reye syndrome
   - Mass lesions
   - Trauma—hemorrhage
     - Epidural
     - Subdural
     - Intraparenchymal
   - Tumors
3. Increased cerebral blood volume
   - Increased CBF
   - Intracerebral vasodilation

ICP (normally <15 mm Hg) is determined by the following variables: cerebrospinal fluid (CSF) volume, cerebral blood volume (CBV), and brain cell volume (Table 9.2). The measurement of ICP and use of CPP as well as oxygen-related monitors to manage severe head trauma are discussed in the section on "Head Trauma".

THE EFFECTS OF HYPOPERFUSION ON BRAIN FUNCTION

Depending on the magnitude and duration, decreased oxygen delivery to brain tissue can cause alterations in CNS function, ranging from agitation to brain death. The sudden cessation of cerebral circulation results in coma in 6–7 seconds, with the cerebral cortex suffering from lack of oxygen before the brainstem. Therefore, the initial state of coma is cortical coma.

Table 9.3 Glasgow Coma Scale

Physical Examination	Points
1. Eye-opening response	
• Spontaneous	4
• To speech	3
• To pain	2
• None	1
2. Verbal response	
• Oriented	5
• Confused, still answers	4
• Inappropriate words	3
• Incomprehensible sounds	2
• None	1
3. Best motor response	
• Obeys	6
• Localizes	5
• Withdraws	4
• Abnormal flexion	3
• Abnormal extension	2
• None	1

The exact duration of absent circulation that will cause irreversible cortical and subsequent brainstem death is controversial.

After TBI, cerebral ischemia is a very early event that usually abates spontaneously or after evacuation of a mass lesion. Acute subdural hematomas and diffuse cerebral edema are at a greater risk for continued cerebral ischemia. The prognosis of patients with persistent ischemia is poor (2).

The relationship between Glasgow Coma Scale (GCS) (Table 9.3) and the $CMRO_2$ in severe head trauma patients can be broadly characterized as follows (GCS <8 = coma) (5):

$CMRO_2$ (normal 3.2)	GCS (normal 15)
1.1	3–4
1.5	5–6
1.5	7–8

Since $CMRO_2$ is primarily determined by CBF, the association of a marked decrease in brain oxygen metabolism with severe neurologic malfunction following trauma suggests that decreased CBF aggravates brain cell dysfunction after trauma.

EFFECTS OF INFLAMMATION ON BRAIN FUNCTION

Inflammation-associated alterations in brain function are linked to both systemic and local inflammatory processes. For instance, systemic inflammation has been associated with decreased CBF, impairment of subcortical and cortical sensory-evoked potential pathways, release of brain injury biomarkers (S–100β and neuron-specific enolase), and decreased brain mitochondrial function (6–9). Encephalopathy during severe systemic inflammation is common and correlated with increased mortality risk (8,10).

TBI is characterized by rupture of the blood brain barrier (BBB) and the leakage of serum components and blood cells into the cerebral tissue that stimulate inflammatory cell migration and activation. These, in turn, engage endogenous microglia, astrocytes, and neurons in cell-to-cell interactions that augment the inflammatory state and the threat to cellular function and viability.

Table 9.4 Etiologies of Coma

1. Cortical
   - A. Metabolic
     - Hypoglycemia
     - Hypoxia
     - Hypercapnia
     - Hyperglycemia
     - Hyponatremia
     - Hypercalcemia
     - Narcotics
     - Barbiturates
     - Diazepam
     - Severe inflammation
     - Liver failure
     - Renal failure
   - B. Infectious
     - Meningitis
     - Encephalitis
   - C. Traumatic
     - Diffuse contusion
     - Subarachnoid bleed
2. Brainstem
   - A. Metabolic
     - Severe hypoxia—brainstem infarct
     - Severe drug overdose
   - B. Traumatic
     - Supratentorial mass
     - Infratentorial mass
     - Direct injury

Activation of inflammatory mediators [especially Interleukin (IL)-6] has been linked to the extent of cerebral damage, BBB malfunction, leukocyte infiltration, and neurological outcome. However, too vigorous suppression of brain injury inflammation can also have detrimental effects on wound healing, cell regeneration, and recovery (11). In this respect, the brain, as with other tissues subjected to tissue injury and inflammation, can suffer from both too much and too little inflammatory response.

ETIOLOGIES OF COMA

Coma is categorized broadly into cortical and brainstem etiologies (Table 9.4). As mentioned previously, the brainstem is much more resistant to metabolic derangements and requires severe metabolic insults (i.e., cardiopulmonary arrest) to malfunction. Most brainstem dysfunction is secondary to nearby or direct traumatic injury or decreased basilar artery blood flow.

Broadly speaking, if physical examination is consistent with an intact brainstem (e.g., normal pupils, normal corneal reflexes, normal extraocular movements), the patient most likely has a cortical and, therefore, a metabolic coma (diffuse cortical trauma may cause similar findings). On the other hand, if any brainstem reflex is abnormal (e.g., one pupil larger and less reactive than the other, diminished corneal reflexes, absence of an extraocular movement), the patient is more likely to have a mass lesion pushing on the brainstem, or direct brainstem injury.

PHYSICAL EXAMINATION OF THE PATIENT WITH ALTERED BRAIN FUNCTION

As with all conditions, physical examination of the patient with neurological malfunction begins with vital signs. Vital signs may also alert the clinician to the presence of underlying neurological injury. Most critically ill patients are tachycardic. Bradycardia is unusual, especially

Table 9.5 Outline of Physical Examination for Brain Status

- Vital signs
- Glasgow Coma Scale
- Pupil reflexes (constriction cranial nerve 3, dilation—entire brain stem)
- Corneal reflexes (cranial nerves 5, 7)
- Oculocaloric or oculovestibular reflexes (cranial nerves 3, 6, 8)
- Posturing response
- Gross motor, upper and lower extremity
- Gross sensory, upper and lower extremity
- Deep tendon and Babinski reflexes

in trauma patients, and may indicate increased ICP or injury to the sympathetic nervous system in the high spinal cord. Similarly, hypertension is less common than hypotension, and can result from increased ICP. Since many critically ill surgical patients are assisted by a ventilator, respiratory status is a less useful indicator of neurological function, except for the broad categories of present or absent.

Physical examination of brain neurological function begins with a global assessment of consciousness. The GCS (Table 9.3) is often used for this purpose, but it does not well describe the evaluation of the barely responsive or unresponsive patient, nor explains the localization of abnormalities. For such circumstances, eliciting brainstem and posturing reflexes can be a valuable adjunct (Table 9.5).

The pupillary reflex depends upon intact sympathetic (dilation from noxious stimuli) and parasympathetic (constriction from light) innervation (Fig. 9.7). The sympathetic nervous system arises in the hypothalamus, above the brainstem, runs through the brainstem, exits from the thoracic spinal cord, and follows the arterial supply to the eye. Constriction of the pupil is secondary to parasympathetic innervation that arises in the midbrain and accompanies the oculomotor nerve to the eye. Corneal reflexes represent sensation by the fifth and motor response by the seventh nerve, both in the pons. Oculovestibular and oculocaloric reflexes (Fig. 9.8) result from stimulation of the vestibular apparatus innervated by the eighth nerve at the ponto-medullary junction with response by the sixth and third nerves connected to the eighth nerve via the medial longitudinal fasciculus. Decorticate rigidity (arms point toward the cortex; Fig. 9.9) to noxious stimuli represents loss of cortical-spinal innervation either from cortical or internal capsule malfunction. Decerebrate rigidity (arms point away from the cortex; Fig. 9.10) usually represents at least partial, bilateral separation of midbrain function from higher centers (1).

Precise documentation of these aspects of the brain neurological examination is mandatory. Potentially confusing terminology such as "doll's eyes" should be avoided. More useful is the statement "Oculovestibular reflex: medial and lateral rectus function bilaterally," which describes precisely the test and the results.

Examination for lateralizing signs (i.e., one side moves differently from the other) is as important for identifying the risk for an intracranial mass lesion as is the recognition of an abnormal brainstem reflex (12).

CNS MALFUNCTION

Head Trauma

Head trauma, especially with coma, requires careful attention to the Airway–Breathing–Circulation (ABC) of resuscitation, as well as an orderly diagnostic approach. This may be difficult when confronted with other major injuries and the hemorrhage and unsightly appearance associated with head injury. Table 9.6 outlines the basic initial clinical approach to the patient with head injury, which may begin at the scene of injury and continue into the intensive care unit (ICU). The injured brain is particularly susceptible to further insults that decrease CBF or increase the local inflammatory reaction. In addition, the brain does not tolerate hypoxia secondary to inadequate pulmonary function. Therefore, rapid and aggressive attention to the

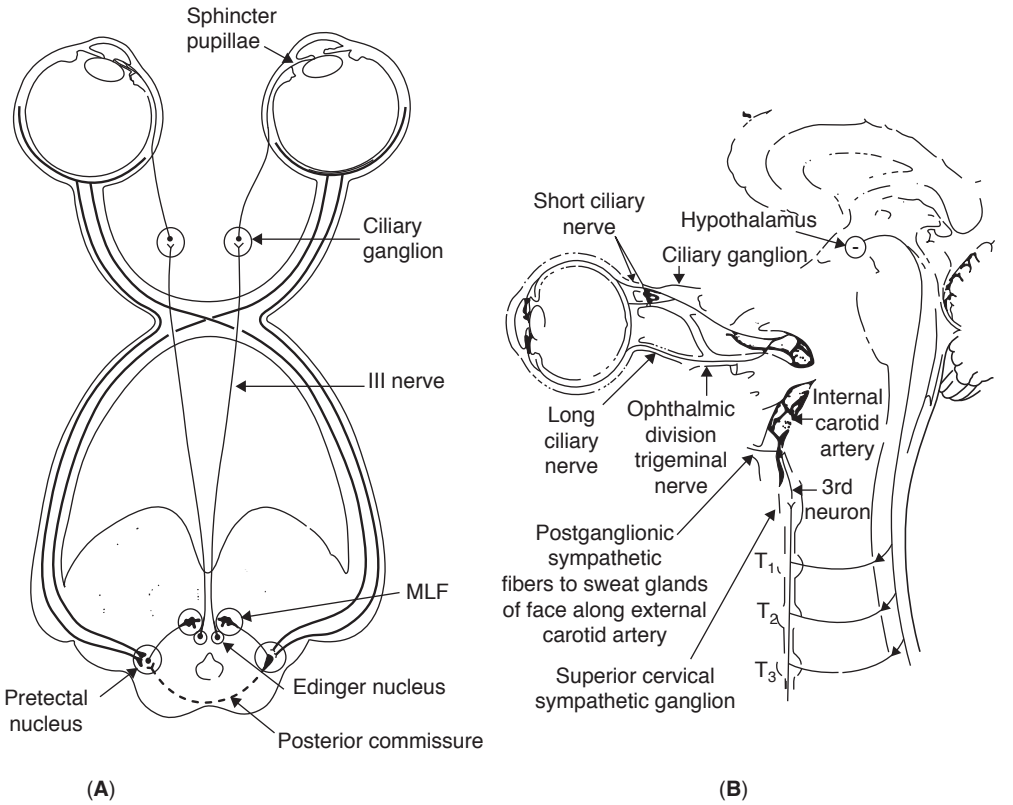

Figure 9.7 A schematic representation of the anatomy of the parasympathetic, pupillary constriction, innervation of the pupil (**A**), and the anatomy of the sympathetic, pupillary dilatation, innervation of the pupil (**B**). Note that the sympathetic system originates in the hypothalamus, above the brainstem, and courses through the brainstem before exiting via the thoracic spinal cord to follow the arterial supply to the eye. *Abbreviation*: MLF, medical longitudinal fasciculus. *Source*: Plum F, Posner JB. The Diagnosis of Stupor and Coma, 3rd edn. Philadelphia, PA: Davis Company, 1982.

ABC of trauma and continuing attention to oxygenation and resuscitation of the circulation are as, if not more, important with brain injury as with any other injured tissues. Previous ideas that brain injury could be limited by providing minimal resuscitation of the circulation are not supported by epidemiologic studies that demonstrate an increased risk of death and neurologic disability in brain-injured patients who suffer from hypotension anytime during the early post-injury period (13–16).

In the comatose patient, an intact brainstem and no lateralizing signs indicate a cortical coma, with little immediate threat to life from the head injury. At the opposite extreme, bilateral mid-position fixed pupils, absent corneal reflexes, and no extraocular movement indicate a severely damaged brainstem with little probability of survival, let alone regaining consciousness (17). Between these extremes would be the comatose patient with an intact brainstem, but with lateralizing arm and/or leg movement that is not secondary to local injury. Following head trauma, such an individual should be considered to have a mass lesion that is potentially reversible, as would a patient with limited brainstem alterations (i.e., one pupil different from the other, different corneal reflexes, a missing extraocular movement). Such patients deserve the highest priority for TBI evaluation [i.e., rapid transport to the computed tomography (CT) scanner], evaluation that may, if necessary, precede other diagnostic efforts (e.g., pelvic radiograph, repeat chest radiograph after chest tube insertion, etc.) (12).

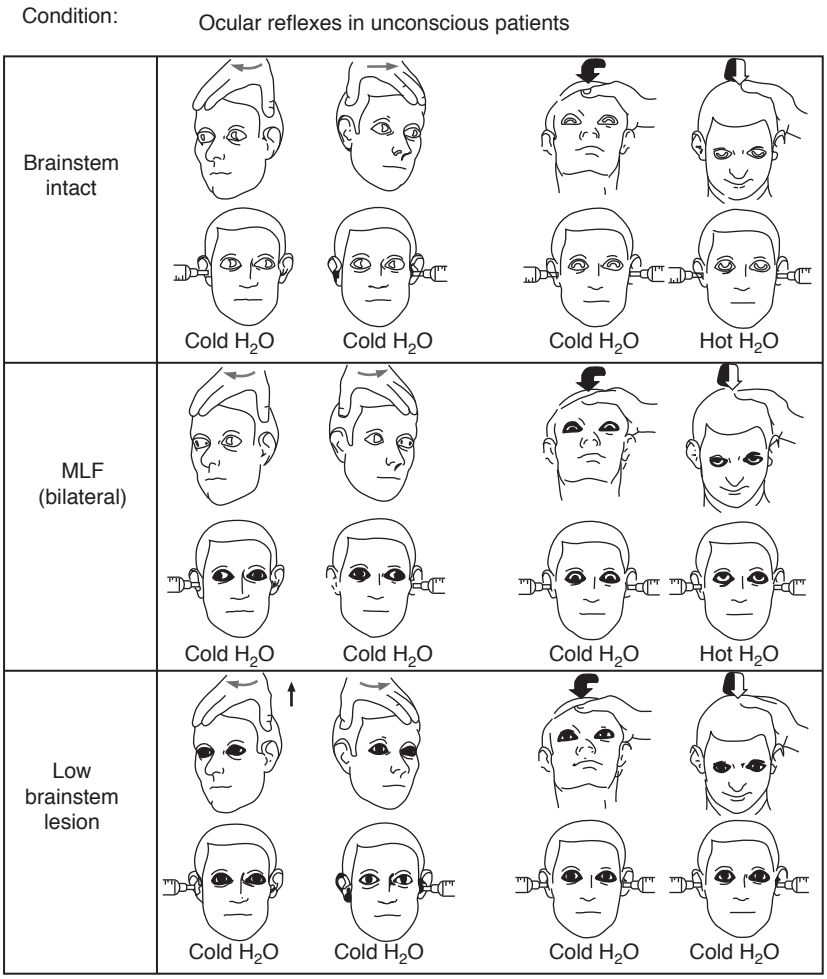

Figure 9.8 A representation of normal oculovestibular and oculocaloric reflexes for a comatose patient with an intact brainstem. The stimulus to the vestibular system innervated by the eighth nerve sends impulses to the sixth nerve in the pons and the third nerve in the midbrain, which then results in conjugate medial and lateral deviation of both eyes. Note that coma is present, and cold stimulation of the tympanic membrane results in deviation of the eyes toward the cold stimulus. *Source*: Plum F, Posner JB. The Diagnosis of Stupor and Coma, 3rd edn. Philadelphia, PA: Davis Company, 1982.

The most common types of head injury are listed in Table 9.7. Any of the supratentorial lesions may result in compression of the brainstem, either laterally (temporal lobe herniation) or symmetrically downward ("coning"). Coma may be secondary to diffuse cortical injury or interruption of the reticular activating system (RAS) in the brainstem. With subtentorial lesions, coma is usually secondary to direct brainstem injury, but cerebellar enlargement may compress the pons producing indirect malfunction. Patients with no direct brainstem injury and little or no cortical injury (e.g., mild cerebral contusion, evacuated epidural hematoma) have the best prognosis.

Today, most patients with documented or suspected brain injury will have a cranial CT scan before or shortly after arrival to ICU. However, even with a "normal" initial CT scan, brain injury may be present that may only be discovered with a follow-up CT scan. In addition, documented CT abnormalities may change despite little clinical difference. Therefore, repeat CT scan is an expected phenomenon in the routine evaluation of head trauma patients (18).

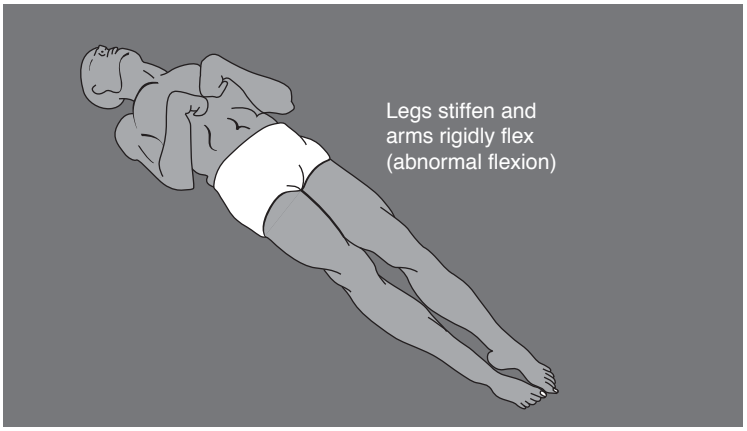

Figure 9.9 A representation of decorticate posturing, with flexion of the upper extremities as the lower extremities extend. *Source*: ACS. ATLS Student Manual. Chicago: ACS, 1997

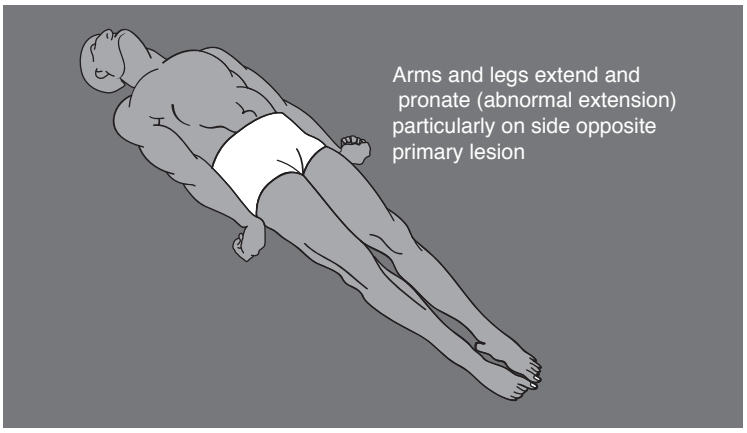

Figure 9.10 A representation of decerebrate posturing, with extension of both upper and lower extremities. *Source*: ACS. ATLS Student Manual. Chicago: ACS, 1997.

Temporal Lobe Herniation

The temporal lobe sits on the tentorium in proximity to the midbrain and the oculomotor nerve. Supratentorial mass lesions (e.g., epidural, subdural, intraparenchymal) push the temporal lobe medially, first compressing the third nerve outside the brainstem, and resulting in an ipsilateral dilated, laterally deviated pupil (the "blown" pupil, Fig. 9.11). This may be associated with contralateral paralysis. Similar findings may be present with early compression of the midbrain proper (1).

Unfortunately, maximum pupillary dilation and lateral deviation are not always present. A pupil may be slightly larger or sluggish, and loss of medial deviation may require testing of extraocular movements. A slightly larger pupil but with good medial deviation of the eye argues against third nerve or midbrain malfunction.

Temporal lobe herniation does not always result in the loss of third nerve function. Again, any unilateral abnormality in brainstem function (e.g., loss of an extraocular movement, different pupils, loss or diminished corneal reflexes) should be considered as evidence of a supratentorial mass laterally impinging upon the brainstem until proved otherwise.

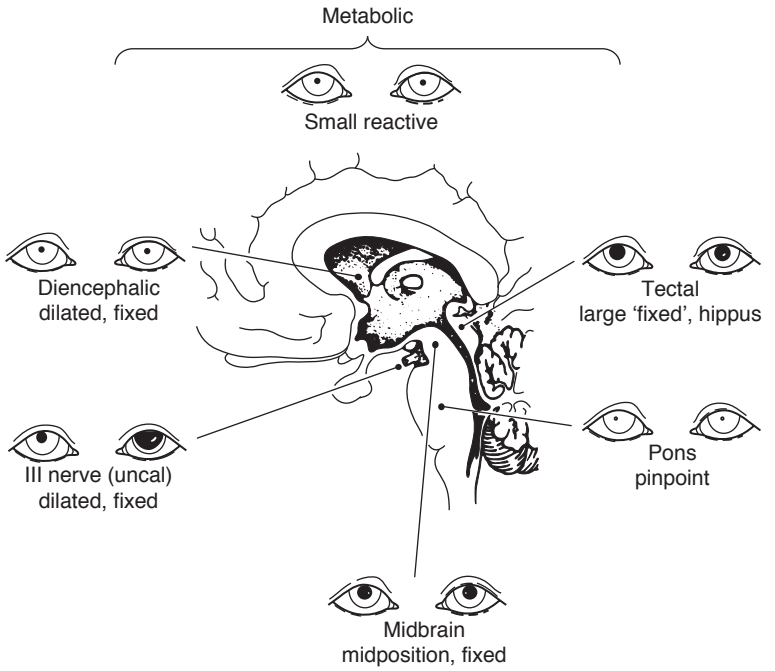

Figure 9.11 A representation of pupillary alterations with coma affecting different regions of the brainstem. With early temporal lobe herniation, the oculomotor nerve is compressed before the midbrain, which may result in the loss of parasympathetic function as well as loss of medial deviation. This figure demonstrates the loss of parasympathetic function with sympathetic function maintained (maximal dilatation), but fails to demonstrate simultaneous lateral deviation, which may also be present. *Source*: Plum F, Posner JB. The Diagnosis of Stupor and Coma, 3rd edn. Philadelphia, PA: Davis Company, 1982.

Symmetrical Downward Brainstem Displacement "Coning"

Symmetrical downward brainstem displacement may result from diffuse bilateral cerebral enlargement, or may follow an initial lateral displacement that subsequently interrupts cerebral circulation. Progressive loss of brainstem function from rostral to caudal is the characteristic sequence, and there is little possibility of function returning following therapy.

Midbrain function is lost first. Interruption of both parasympathetic and sympathetic pupil innervations results in mid-position, fixed pupils that are often characterized as fixed and dilated (Fig. 9.11). (One should remember that this is not maximal dilation, and that especially when sympathomimetic drugs are used, such as epinephrine and dopamine, maximal dilation may be present with or without brainstem injury). Spontaneous lateral eye deviation is rare and sixth nerve function may be elicited only with oculovestibular or oculocaloric reflexes. Corneal reflexes will be present.

Pontine function is lost later as evidenced by no corneal reflexes and no extraocular movement. Subsequently, medullary centers are destroyed with loss of gag reflex and respiration.

Basilar Skull Fracture

Physical examination is usually sufficient to diagnose basilar skull fracture (Table 9.8). CSF mixed with blood from either the nose or an ear is determined by placing the liquid on a piece of filter paper. CSF will migrate more rapidly than blood, producing a "ring" around the blood. Patients with basilar skull fractures have a communication of CSF with the environment and are at greater risk of developing a CSF infection. Also, with evidence of frontal sinus fracture, passage of nasogastric or nasotracheal tubes should be avoided or performed with great care to prevent intracranial passage of these devices.

Table 9.6 Clinical Assessment of Head Trauma

1. ABC of resuscitation
2. Determination of level of consciousness (Glasgow Coma Scale)
3. Examination of brainstem
4. Examination for lateralizing signs
5. Examination of skull and face
6. CT scan of head and neck

Table 9.7 Categories of Head Injury

1. Supratentorial
   - Cerebral contusion
   - Diffuse axonal injury
   - Epidural hematoma
   - Subdural hematoma
   - Intraparenchymal bleeding
2. Subtentorial
   - Cerebellar contusion and/or hemorrhage
   - Brainstem contusion and/or hemorrhage

Table 9.8 Basilar Skull Fracture

- Battle sign ecchymosis behind ear
- Hemotympanum
- Bilateral periorbital ecchymosis
- CSF mixed with blood

ICP and Brain Oxygenation Monitoring: Maintenance of CPP and Brain Oxygenation

ICP and CPP measurement are commonly used tools to assist the management of head trauma. The different methods and their respective benefits and limits will not be discussed. Instead, indications and general measures used to reduce ICP and increase CPP will be presented.

The common indications for ICP monitoring in head trauma are listed in Table 9.9. In general, ICP monitoring is of little use once severe brainstem injury has occurred, and is used instead to indicate the possibility of new, reversible supratentorial bleeding or institute therapy in an attempt to avoid secondary brain injury from decreased CBF.

ICP and CPP monitoring can provide prognostic information. When aggressive attempts are used to manage ICP and CPP, poor outcome correlates directly with the highest ICP as well as the duration of time the ICP is >20 mm Hg and CPP <60 mm Hg (19). Successful lowering of the ICP and increasing CPP using surgical intervention and/or medical therapy is associated with a better outcome than either no therapy or therapy that is not successful (20).

Methods used to reduce ICP are listed in Table 9.10 and are generally used for ICP >20 mm Hg (19). Resuscitation with albumin as compared to isotonic saline with the presumption that a higher oncotic pressure would decrease the risk of secondary brain injury has not been supported in patients with severe brain injury (21). Hypertonic saline (HTS), however, using both a bolus and continuous management strategy has been effective as long as attention to increased serum sodium concentrations (i.e., >155 meq/L) and osmolality (>320 mOsm/L) are provided. Mannitol use is subject to similar constraints, but is used principally in a bolus fashion (22–25).

Drainage of CSF via a device in a cerebral ventricle (ventriculostomy catheter that also measures ICP) can acutely lower ICP (20). Hyperventilation to an arterial pCO_2 < 35 mm Hg is used as an acute measure for patients who might be suffering acute progression from a mass lesion.

Drug-induced coma has a limited role, planning to use short-acting barbiturates when the other strategies are unsuccessful (22,26).

Table 9.9 Common Indications for Intracranial Pressure Monitoring Glasgow Coma Scale ≤8

- Early warning of potentially reversible new mass lesion
- Reduction in secondary brain injury

Table 9.10 Methods to Reduce Intracranial Pressure

1. Elevate head of bed
2. Increase serum osmolality
   - Mannitol
   - Hypertonic saline
3. CSF drainage
4. Hyperventilation (pCO_2 30–33 mm Hg)
   Rarely used, usually for acute deterioration
5. Drug induced coma
6. Decompressive craniectomy
7. Decompressive laparotomy

Decompressive craniectomy has regained stature in the last two decades as a viable management strategy in selected patients. Young patients with early intervention appear to exhibit the greatest potential benefit (22,25).

As described in the chapter 5, intra-abdominal hypertension (IAH) as a consequence of abdominal injury and/or fluid sequestration in the abdominal compartment can increase central venous pressure (CVP). An increase in CVP can also result in an increase in ICP. Decompressive laparotomy for IAH has been shown to reduce ICP even in the absence of the abdominal compartment syndrome (27–29). Therefore, monitoring intra-abdominal pressure can be a practical adjunct to ICP management during surgical critical illness.

The other approach to maintaining CPP > 60 mm Hg is the elevation of MAP, an approach that may be of value even when ICP is elevated (20). The first principle for maintaining MAP is to ensure excellent resuscitation of the circulation by maintaining normal intravascular volume (30). MAP can also be elevated using vasoconstrictor and/or inotropic drug administration. Norepinephrine may be superior to dopamine for this indication (22,31).

As mentioned above, the relationship of ICP and CPP monitoring and manipulation to more direct measures of CBF, oxygen provision and utilization, as well as brain cell metabolism are under study. Such monitors may allow more precise adjustments in CPP parameters, in a case-by-case manner, rather than the more generic limits currently employed (32,33).

Adjuncts in the Management of Traumatic Brain Injury (Table 9.11)

Many older patients who suffer head and/or spine injuries are anticoagulated with warfarin and drugs that inhibit platelet function. Such anticoagulation is associated with worse outcome as compared to non-anticoagulated patients (34,35). By inference, rapid reversal of this anticoagulation is indicated with the hope that this will limit the severity of hemorrhage and nerve tissue injury. In addition, patients with an admission platelet count <100,000/mm^3 are at a high risk for mortality and those with a platelet count <175,000/mm^3 are at greater risk for intracranial hemorrhage progression. These epidemiologic data raise the possibilty of benefit from early platelet administration for relative thrombocytopenia as well as drug-induced platelet inhibition (36).

Beta-blocker (BB) therapy is common for patients prior to injury and after hospital admission following injury. Under both circumstances, epidemiologic data suggest reduced mortality following TBI (37,38). As cautioned in a recent review, however, these data are at present insufficient to recommend routine BB administration following TBI (25).

Table 9.11 Adjuncts for the Management of Traumatic Brain Injury

I.	Reversal of anticoagulation
	Fresh frozen plasma and vitamin K
	Administration of platelets
II.	Beta-blocker exposure

As evidenced in the general trauma population, early enteral nutrition (beginning day 1 after injury) is associated with improved neurological outcomes (39).

TBI-Associated Organ Malfunction (Table 9.12)

Diabetes Insipidus

Diabetes insipidus has a reported incidence range of 3–51% following TBI, with the diagnosis more common in patients with severe TBI, cerebral edema on head CT, and is associated with increased mortality risk (40). A large urine output (>90 cm^3/kg/day) combined with a low urine specific gravity (<1.010), a low urine osmolality (50–200 mOsm/L), and an elevated serum sodium and/or serum osmolality (>300 mOsm/L) usually suffice to make the diagnosis.

While longer-lasting vasopressin administration is effective after the acute post-injury time frame, patients who have marginal hemodynamics and an ongoing risk of blood volume depletion can be effectively managed with the continuous infusion of vasopressin (41). Regardless of management strategy, continuing monitoring of serum sodium and osmolality is necessary in the ensuing days and sometimes weeks, either because of persistence of the non-physiologic diuresis or resolution of the alteration (40).

Coagulation Disorders

While many patients suffering from TBI have been receiving anticoagulation medications, TBI itself can result in severe coagulation abnormalities. Platelet counts <100–150,000/mm^3, prolongation of the international normalized ratio (INR >1.4) and activated partial thromboplastin time (aPTT >38.4 seconds) have all been documented following TBI and are associated with hypotension on admission, subarachnoid hemorrhage, cerebral edema, midline shift, progression of intracranial hemorrhage, and higher mortality (42–44). These alterations may be present on admission or develop over the next few days, demanding repetitive monitoring. One study suggests that reversal of the protein coagulation deficits with recombinant factor VIIa is particularly useful (45).

At the opposite end of the spectrum, TBI is associated with an increase in deep vein thrombosis frequency (46). This epidemiology and the controversies related to prophylactic anticoagulation for pulmonary embolism prevention are addressed in chapter 10.

Acute Lung Injury

Acute lung injury (ALI) has been reported in as many as 35% of patients with critical neurological illness (47). In the setting of TBI, acute lung injury is associated with an increased mortality risk (48). Two mechanisms of ALI-associated pulmonary edema have been described, hydrostatic and non-hydrostatic, with hydrostatic being more common (49,50). An increase in pulmonary capillary pressure from alterations such as pulmonary venous constriction and acute myocardial depression have been invoked as etiologies of increased hydrostatic pressure (50,51). Non-hydrostatic pulmonary edema has been linked to the release of brain injury inflammatory mediators into the systemic circulation as well as more severe deficits in oxygenation (49,50).

The management of ALI in the setting of TBI is the same as described in the chapter 6. Precision in making a hemodynamic diagnosis is key since presumption of a hydrostatic mechanism and overzealous depletion of intravascular volume could result in a secondary brain insult from brain hypoperfusion.

Table 9.12 TBI-Associated Organ Malfunction

Diabetes insipidus
Coagulation disorders
Acute lung injury
Myocardial depression
Hypoadrenalism

Myocardial Dysfunction

Alterations in myocardial function from arrhythmias to cardiogenic shock have been associated with intracranial insults, most characteristically, subarachnoid hemorrhage, but such cases have been reported with TBI without a subarachnoid component. While TBI can be associated with anatomic myocardial damage, usually the myocardial malfunction is physiologic and can abate over a few days. The management is the same as described in the chapter 3, once again necessitating a precise hemodynamic diagnosis for proper management (51–53).

Hypoadrenalism

A definition of hypoadrenalism can be met in as many as 50% of patients with moderate to severe TBI. Meeting the definition is associated with more vasopressor use and may be linked to higher IL-6 blood concentrations (54,55). Since the infusion of exogenous hydrocortisone typically improves MAP during severe systemic inflammation, replacement or super-physiologic dosing might decrease the magnitude and/or duration of vasopressor use in TBI patients who meet a hypoadrenalism definition (56). However, at present, no prospective, randomized study has investigated the administration of exogenous hydrocortisone to these patients.

Blunt Cerebrovascular Injury

Signs and symptoms of as well as risk factors for blunt cerebrovascular injury (BCVI) are listed in Table 9.13 (57–59). Screening such patients with 16-channel computed tomography angiogram is the diagnostic method of choice. For carotid injury, prognosis is linked to the grade of injury (Table 9.14), an association that does not hold for vertebral artery damage (57,58). Management strategies include antithrombotic treatment, endovascular treatment, and open surgery. Treatment decision making is difficult in the face of other injuries, especially TBI, and the potential for bleeding complications. Antiplatelet therapy for most injuries is gaining favor with endovascular treatment for acute stroke, recurrent symptoms despite antithrombotic treatment, or enlarging traumatic aneurysms. Open surgery is principally directed to active hemorrhage from the extrcranial carotid (57,58).

Spinal Cord Injury

Spinal cord injury should always be suspected in any trauma victim and requires careful evaluation of neurological examination and radiographic information. ICU personnel may receive a patient after emergency surgery that precluded such evaluation preoperatively.

Neurologic findings that suggest spinal cord injury are listed in Table 9.15. Warm extremities with hypotension can follow interruption of sympathetic-mediated vasoconstriction and decreased systemic vascular resistance rather than diminished cardiac output. Therefore, this "neurogenic" hypotension is not indicative of shock from inadequate oxygen delivery and does not require aggressive resuscitation unless there is an associated brain injury that will require measures to maintain the CPP. Under these circumstances, a vasoconstrictor may be necessary to overcome the non-physiologic decrease in systemic resistance.

True shock can be present with spinal cord injury, and obviously the presence of paraplegia or quadriplegia does not preclude hypotension that is associated with insufficient oxygen delivery to meet cellular demands. Therefore, the presence of warm hands and feet does not obviate the necessity of looking for markers of "the rude unhinging." The application of

Table 9.13 Blunt Cerebrovascular Injury

I.	Signs and symptoms
	Arterial hemorrhage from neck/nose/mouth
	Expanding cervical hematoma
	Cervical bruit in patient <50 years old
	Focal neurological deficit
	TIA
	Hemiparesis
	Horner's syndrome
	Stroke on CT or MRI
	Neurological deficit inconsistent with CT findings
II.	Risk factors for BCVI
	High energy transfer, likely hyperextension with rotation or hyperflexion
	Displaced mid-face fracture
	Basilar skull fracture with carotid canal involvement
	Closed head injury with DAI and GCS ≤6
	Near hanging
	Severe thoracic injury

Table 9.14 BCVI Grading Scale

I.	Luminal irregularity or dissection with <25% narrowing
II.	Dissection or intramural hematoma with ≥25% narrowing, intramural thrombus, or raised intimal flap
III.	Pseudoaneurysm
IV.	Occlusion
V.	Transection with free extravasation

vasoconstrictor agents when oxygen delivery is insufficient can result in further deficits in oxygen supply and utilization. Consequently, the early evaluation of hypotension following spinal cord injury includes monitors such as mental status, urine volume, base deficit, serum potassium, serum glucose, lactic acid, and ionized calcium (see chaps. 2 and 3).

Neuromuscular Disorder of Surgical Critical Illness

Critical illness polyneuropathy and myopathy have been recognized mechanisms of decreased muscular strength for at least three decades. This illness is distinct from other neuromuscular conditions such as Guillain–Barre´ syndrome, antibiotic toxicity, competitive neuromuscular blocking agent neuropathy, and cachectic myopathy (60). Risk factors for this condition are severe systemic inflammation and persistent glucose elevation above 170 g/dl (61,62). Electrophysiologic studies are necessary to confirm the diagnosis that may take weeks to months for resolution.

Most frequently, recognition of this disorder accompanies mechanical difficulties during ventilator weaning (e.g., persistently low tidal volumes, carbon dioxide retention). Establishing the diagnosis allows better understanding of the necessity for continuing ventilator support. There is no treatment for this condition save for the management of systemic inflammation and, possibly, glucose regulation. With time, there is usually sufficient recovery of function to be liberated from a ventilator.

Management Priorities for Patients with TBI

Close collaboration between the surgical critical care specialist, neurosurgery, orthopedic surgery, trauma surgery, and anesthesiology is no more necessary than in the TBI patient with multiple other injuries. TBI outcome is adversely affected by episodes of hypotension and hypoxia, especially in the first hours following injury. Obviously, early surgery to control

Table 9.15 Neurologic Findings with Spinal Cord Injury

- Symmetrical loss of motor function
- Symmetrical loss of sensation
- Flaccid areflexia
- Warm extremities with hypotension

hemorrhage (e.g., emergency splenectomy vs. non-operative management), would be considered a method of improving TBI recovery. Orthopedic surgery that does not address hemorrhage would not be indicated when shock and/or severe hypoxia are present.

More controversial is the early (<24 hours after injury) application of orthopedic intervention in resuscitated individuals and the risk of worsening TBI mortality and functional status in survivors (63–65). Surgical intervention does pose the risk of hypotension from induction of anesthesia and blood loss as well as hypoxia from such mechanisms as the fat embolism syndrome, both of which might initiate and/or aggravate secondary brain injury (66).

The concept of "damage control orthopedics" (DCO) has emerged as a technique that is more aggressive than splinting and/or traction, but less aggressive than internal stabilization. Typically, DCO consists of external stabilization for the fracture site accompanied by wound irrigation when an open fracture is present.

Pending additional clinical investigation, application of management priorities linked to the severity of TBI seems logical. Early "total care", that is, internal stabilization, of orthopedic injuries would proceed for patients with mild TBI (GCS 14–15) and a normal head CT. DCO would apply for patients with a GCS <8. DCO would be "considered" for patients with a GCS of 9–13 and intracranial pathology, especially if ongoing resuscitative efforts (treatment of coagulopathy, reversal of hypothermia, and vasoconstrictor use to maintain CPP) were in place (66).

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10 | The hematopoietic system

Hematopoietic system topics that are most frequently encountered in surgical critical illness are listed in Table 10.1.

SUBMASSIVE TRANSFUSION

The most common reason for the administration of blood products is the submassive loss of red blood cells (RBCs) or the reversal of a hypocoagulopathy that may be either disease- or therapy-induced. The potential adverse effects of RBC transfusion are listed in Table 10.2 (1–7). Many of the adverse effects appear to be linked to the presence of leukocytes in the RBC transfusion, and several may be ameliorated by processing that results in a more effective leukoreduction (1,3,6). Whether or not such a strategy will diminish the incidence of mortality and multisystem organ failure following submassive RBC transfusion remains to be determined.

The recognition of these adverse effects has accompanied the almost simultaneous realization that blood oxygen content can be reduced to nearly 50% of normal (decreased hemoglobin concentration from 14 to 7 g/dl) without a measurable decreased in tissue oxygenation parameters during surgical critical illness in the Flow Phase of shock. The important issue in this realization is that achievement of the Flow Phase of shock with augmented oxygen delivery and consumption must then depend upon an enhanced circulation, i.e., increased cardiac output, rather than more blood oxygen content (see chaps. 2 and 3) (5).

Clinical practice guidelines for the transfusion of red cells in adult trauma and critical care have been well described (Table 10.3) (8). Most controversial is the use of RBC administration during early goal-directed resuscitation of sepsis where the published protocol included RBC transfusion if the venous oxygen saturation end point was not achieved through crystalloid infusion alone (9). Two-thirds of the goal-directed group received an RBC transfusion as compared to 44% of the control group, and there was a survival advantage to the goal-directed strategy (5). This advantage does not appear to continue after resuscitation endpoints are achieved (8).

Table 10.4 has a listing of potential adverse reactions to fresh frozen plasma (FFP), cryoprecipitate, and platelet (PLT) transfusion (10–15). FFP that is ABO-compatible rather than ABO-identical appears to augment risk, suggesting that when feasible, the ABO-identical FFP be selected (16).

Traumatic brain injury is the most common indication for FFP and/or PLT transfusion in submassive transfusion, and, typically, in the setting of drugs that cause coagulopathy (warfarin and/or anti-platelet agents). As noted in the chapter 9, the administration of FFP and PLT under these circumstances is beneficial (17,18). However, as the adverse possibilities of FFP and PLT administration are noted, the submassive application of these products demands caution and well-delineated indications, like those developed for RBC transfusion.

MASSIVE TRANSFUSION IN TRAUMA

Massive transfusion (MT) in trauma is most often defined as the administration of >10 units of RBCs in the first 24 hours after injury. Some authors restrict MT to patients who receive this volume in the first six hours (16,19). As expected, MT is associated with higher injury severity, hypotension (<70 gm Hg systolic), hypothermia (<34 C), and metabolic acidosis (pH <7.1) (19–21). While in the past, coagulopathy was considered dilutional and/or a consequence of fluid and RBC administration, more recent data demonstrate that coagulopathy (especially an international normalized ratio >1.5) is usually present shortly after injury in patients who will receive MT (19,20).

Therefore, the MT patient often exhibits the "triangle of death" at the time of or shortly after Emergency Department admission. While efforts to control hemorrhage are the mainstay

Table 10.1 Surgical Critical Illness Hematopoietic Topics

I. Blood product transfusion
   A. Submassive
   B. Massive
II. Coagulation disorders
   A. Hypocoagulation
   B. Hypercoagulation

Table 10.2 Potential Adverse Effects of Red Cell Transfusion

I. Fever
   A. Alloimmunization from transfused leukocytes
   B. ABO incompatibility—rare
   C. Contamination—rare
II. Leukocytosis—reduced by filtration of leukocytes
III. Immunosuppression and new infection (especially blood >12 days old)
IV. Transfusion associated acute lung injury (TRALI)
V. Multisystem organ malfunction

Table 10.3 Guidelines for Red Cell Transfusion

I. General critical illness
   A. Hemorrhagic shock (active bleeding and Ebb phase)
   B. Restrictive strategy (transfuse for hemoglobin (Hgb) <7 g/dl) is indicated for flow phase patients. May transfuse for Hgb >7, <10 g/dl for acute myocardial ischemia and/or new onset sepsis, especially in Ebb phase
   C. Do not use Hgb only as the trigger—use overall assessment of oxygen delivery and consumption
   D. Can use single unit transfusion
II. Sepsis
   A. First six hours—if central venous oxygen saturation is not 70% or greater after fluid infusion, then RBC transfusion to a hematocrit of 30% is acceptable (patient remains in the Ebb phase).
   B. Later sepsis—transfuse if Hgb < 7 g/dl
III. Risk or presence of acute lung injury and/or ARDS
   A. Avoid transfusion
   B. Report possible TRALI event
IV. Traumatic brain injury
   A. No benefit for transfusion for Hgb 7–10 g/dl range

Table 10.4 Adverse Effects of Fresh Frozen Plasma/Cryoprecipitate and Platelet Transfusion

I. Fresh frozen plasma/cryoprecipitate
   A. Fever
   B. Immunosuppression and increased infection risk
   C. Multisystem organ failure
   D. TRALI
   E. Infection transmission
II. Platelets
   A. Fever
   B. Allergic—rash
   C. Infection transmission
   D. TRALI

Table 10.5 Common Causes of Disseminated Intravascular Coagulation in Surgical Critical Illness

I. Systemic Inflammation
II. Malignancy
III. Obstetrical calamities
A. Amniotic fluid embolism
B. Abruptio placentae

of management (see chap. 5), anticipation of coagulopathy, and early and aggressive administration of coagulation factors (FFP, PLT) in a 1:1:1 ratio with RBC is associated with decreased mortality from early exsanguination as well as that extending out to 48 hours (20,22,23).

Concomitant efforts to improve total body oxygen delivery, increase body temperature, and decrease metabolic acidosis can result in physiologic improvement in coagulation as well as vital cell function (19,21,24). This combination of the administration of coagulation factors and the reversal of metabolic acidosis and hypothermia fall under the rubric of "damage control resuscitation," and should be continued until the MT process has abated, typically about 24 hours.

Anticipation of MT is key, with early use of FFP in trauma patients who receive RBC. Patients arriving in the Emergency Department with a history of severe hypotension, blood transfusion already underway, and/or hypothermia on arrival are candidates for 1:1 FFP. Once this is underway, the plans for platelet administration can follow, especially with platelet concentrates that allow a 4–6 unit "pack" to be provided for every 4–6 units of RBC.

COAGULATION DISORDERS IN SURGICAL CRITICAL ILLNESS

Hypocoagulation

Hypocoagulation that is not of the magnitude linked to massive transfusion is common in surgical critical illness. Tissue injury can cause endothelial microtears that result in coagulation factor activation and platelet consumption. Simultaneously, fibrinolysis is activated and augmented, especially in tissues subjected to ischemia. Therefore, tissue injury, the Ebb Phase of shock, and inflammation from tissue injury can combine to establish a hypocoagulable state characterized by prolongation of coagulation protein cascades, decreased platelet count, and increased fibrin degradation product production (25). Among the sites of tissue injury, brain tissue disruption is particularly capable of causing a hypocoagulable state (21).

This combination of coagulation alterations is similar to those listed with the diagnosis of disseminated intravascular coagulation (DIC). DIC has been principally linked to severe systemic inflammation and includes a documented reduction in fibrinogen blood level along with thrombocytopenia, increased fibrin degradation product concentration, and a prolonged prothrombin time. DIC can result in microvascular thrombosis and associated organ malfunction that appears to parallel the severity of DIC as much as the severity of systemic inflammation (26). The principal management strategy is to treat the underlying cause (Table 10.5) (27).

Thrombocytopenia (platelet count $<150 \times 10^9$/L) is common in critical illness (30–40%), attributed to such mechanisms as listed in Table 10.6, along with DIC (28,29). Regardless of the mechanism, thrombocytopenia is associated with a poor outcome. After an initial nadir at about intensive care unit day 4, a gradual increase in platelet count is a good prognostic indicator, especially if the increase exceeds the value measured during the first intensive care unit day (28).

Heparin-induced thrombocytopenia (HIT) is divided into two types: a non-immune mediated form (type I) and an immune-mediated form (type II, see below), Type I is a benign alteration that can be observed in up to 25% of patients, beginning early (days 1–4) after heparin administration. Usually, the thrombocytopenia is mild ($100–130 \times 10^9$/L), transient, and asymptomatic. This may be caused by platelet agglutination (30).

Table 10.6 Coagulation Disorders in Surgical Critical Illness

I. Hypocoagulation
  A. Tissue injury
  B. DIC
  C. Thrombocytopenia
  1. Disease induced
    A. Bone marrow depression
    B. Sequestration in tissues
    C. Hemorrhage
  2. Heparin induced thrombocytopenia
    Non-immune mediated (type I)
II. Hypercoagulation
  A. Heparin induced thrombocytopenia
    Immune mediated (type II)
  B. Tissue injury
    i. Increased tissue factor-dependent thrombin production
    ii. Decreased protein C and antithrombin III concentrations

Hypercoagulation

Type II HIT is a pro-thrombotic, antibody-mediated process that usually develops after 5 days of heparin administration. HIT is characterized by platelet consumption and thrombosis from active thrombin generation and tissue factor expression (30).

A diagnosis of type II HIT should be considered when the platelet count decreases to $<150 \times 10^9$/L or >50% from baseline, beginning 5–14 days after heparin exposure. Rapid-onset type II HIT can develop within 24 hours in a previously sensitized individual. Delayed onset is rare, but can develop days or weeks after discontinuing heparin. In these delayed circumstances, thrombocytopenia may or may not be present, but appears quickly if heparin is re-introduced (29,30).

The estimated incidence of type II HIT is 0.1–5%, with risk increased by bovine as compared to porcine unfractionated heparin (UFH) and with the least risk associated with low-molecular-weight heparin (LMWH). Risk is also increased by the duration of use, especially previous exposure within 100 days, surgery, and female sex (30).

The most worrisome feature of type II HIT is the prothrombotic state that can result in venous and/or arterial thrombosis. DVT, pulmonary embolism, skin necrosis, thrombotic stroke, limb ischemia, and myocardial infarction are all associated with it (29).

Monitoring of platelet count is the principal screening tool for the diagnosis of type II HIT. A baseline value is recommended for all patients who will receive any form of heparin, and again within 24 hours if there has been recent prior exposure. Subsequently, monitoring every other day between days 4 and 14 will likely identify patients for potential HIT testing. Regardless of routine testing, any new thrombotic event (venous or arterial) in a patient receiving heparin should prompt measurement of the platelet count.

Since many patients develop heparin antibodies and do not develop thrombocytopenia or clinical HIT, a clinicopathological approach to testing for HIT is recommended. Using a ranking tool like the "4 Ts" scoring system (Table 10.7) may assist in selecting patients for investigation (29,30).

Both enzyme-linked immunosorbent and platelet activation assay tests are available to test for the presence of antibody. Both are highly sensitive, so negative results are useful for ruling out type II HIT. Positive results must be juxtaposed to the clinical state of the patient (29,30).

The treatment of type II HIT is outlined in Table 10.8. Importantly, platelet transfusion can augment thrombosis risk, vitamin K antagonists can deplete intrinsic anticoagulants (proteins C and S), and inferior vena cava (IVC) filter placement can result in massive IVC thrombosis if alternative anticoagulation is not in place (30).

Table 10.7 The 4 T Scoring System for HIT Diagnosis

	Score		
Definitions	**2 Points**	**1 Point**	**0 Points**
Thrombocytopenia	>50% decrease, nadir >20k	30–50% decrease, nadir 10–19k	<30% decrease, nadir <10k
Timing	5–10 days ≤1 day with recent heparin (past 30 days)	> day 10 <1 day with no recent (31–100 days)	< day 4 No recent heparin
Thrombosis	New venous or arterial or skin necrosis	Progressive or recurrent	None
Other causes	None	Possible	Definite
Pre-test probability of positive testing			
Score		**Rank**	
6–8		High	
4–5		Intermediate	
0–3		Low	

Table 10.8 Treatment of Type II HIT

I. Discontinuation of all heparin administration
   A. Line flushes
   B. Heparin-coated catheters
   C. Sub Q or IV dosing
II. Do note provide platelet transfusion
III. Discontinue vitamin K antagonists (VKAs)
IV. Alternative anticoagulation
   A. Lepirudin
   B. Argatroban
   C. Bivalirudin
   D. Danaparoid
   E. Fondaparinux
V. Investigate for DVT
VI. Restart or initiate VKA after platelet count recovery (150k)

Much more common than type II HIT is the hypercoagulable state associated with tissue injury. Therefore, tissue injury can result in both decreased and increased coagulant functions. Most often, surgical critical illness, per se, is associated with an increased risk of venous rather than arterial thrombosis. Classically, Virchow's triad of stasis (decreased blood flow in a vein), injury (direct injury to a vein), and hypercoagulable state is regularly applicable to surgical critical illness and highlights the preventable features of venous thrombosis.

Regional and/or global hypoperfusion results in stasis, trauma (that includes venous cannulation) results in vein injury, and tissue injury distant from a vein can result in a hypercoagulable state. The hypercoagulable state from tissue injury is associated with increased tissue factor (TF)-dependent thrombin generation as well as decreased protein C and antithrombin III blood concentrations (31).

Screening for DVT in surgical critical illness with duplex ultrasound is controversial (32). As expected, routine screening protocols result in more frequent DVT diagnosis, especially in trauma patients. Risk factors associated with DVT diagnosis in this setting are: age >40 years, extremity injury, head injury, venous injury, major surgery, and ventilator days >3 (33). Whether or not initiation of therapy for DVT based upon a screening diagnosis improves the outcome has not been sufficiently studied.

Table 10.9 DVT/PE High-Risk Trauma Patients

I.	Spinal cord injury, especially high thoracic, with paresis
II.	Complex pelvic fractures
III.	Multiple long bone fractures
IV.	Head trauma with GCS <8
V.	Cardiopulmonary compromise
VI.	Age >45

Prophylaxis for DVT formation in surgical critical illness addresses all aspects of Virchow's triad. Stasis is avoided by rapid restoration of the global circulation as well as regional augmentation to the lower extremities (compressive devices). Vein injury is decreased by early removal of catheters (especially in the femoral vein). The hypercoagulable state is treated by increasing antithrombin III and anti-activated factor X (Xa) effect with prophylactic UFH and LMWH, respectively.

Retrospective data suggest that LMWH can be safely administered to patients with blunt solid abdominal injuries despite a plan for non-operative management. Even when prophylaxis is provided early (<3 days after injury), LMWH does not appear to be associated with failure of non-operative strategies (34). Interestingly, concern has been raised that standard prophylaxis dosing with LMWH may not be sufficient to provide an effective elevation in anti-factor Xa blood levels for patients with surgical critical illness (35).

Prophylactic heparin administration is most controversial in the setting of traumatic brain injury (TBI) (36). Recent retrospective data suggest that LMWH (initiated in the first 48 hours) is both safer and more effective than UFH in the setting of TBI (37). However, the incidence of DVT in TBI is sufficiently high such that DVT screening is recommended even when prophylaxis is provided (38).

Spinal cord injury is associated with a diagnosis of venous thromboembolism (VTE) in as many as 65% of the cases when patients are systematically investigated with venography and/or compression duplex ultrasound, despite the use of heparin prophylaxis. Under these circumstances, a diagnosis of "major" VTE (DVT in a popliteal vein or more proximal and/or pulmonary embolism) is evident in as many as 16% (39). This high incidence and the potential for bleeding complications have prompted use of IVC filters for prophylaxis in this as well as other trauma populations considered at high risk, especially if anticoagulation of any type is contraindicated (Table 10.9) (40,41).

At present, the decision to place an IVC filter for pulmonary embolism prophylaxis during surgical critical illness is driven by a risk-benefit analysis on a case-to-case basis. Plans for a prospective randomized study of IVC filter placement in high-risk trauma patients may provide better data for this decision process (42).

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The Clinical Handbook for Surgical Critical Care

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The Clinical Handbook for Surgical Critical Care, Second Edition, covers the principle aspects of acute and ongoing care for the critically ill surgical or trauma patient residing in the ICU. This new edition is separated into chapters by organ systems, and reviews the critical disease states associated with these organs. All chapters follow the same structure of; pathophysiology, physical examination and monitoring, laboratory results, and treatment options (with supporting evidence).

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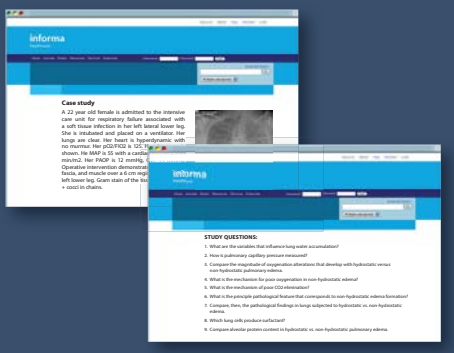

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ISBN 978-184184922-5